Saccadic direction errors are associated with impulsive compulsive behaviours in Parkinson's disease patients.

Authors

Dr Pedro Barbosa[1,2], Dr Diego Kaski[3,4], Ms Patricia Castro[5], Prof Andrew J Lees[1], Prof Thomas T Warner[1,2*], Dr Atbin Djamshidian[1,6*]

Affiliation

1. Reta Lila Weston Institute of Neurological Studies, UCL Queen Square Institute of Neurology, University College London, London, UK
2. The National Hospital for Neurology and Neurosurgery, Queen Square, London, UK
3. Department of Clinical and Movement Neurosciences, 33 Queen Square, University College London, London
4. Department of Neuro-otology, Charing Cross Hospital, Imperial College London, London
5. Escuela de Fonoaudiologia, Facultad de Medicina, Clinica Alemana Universidad del Desarrollo, Santiago, Chile
6. Department of Neurology, Innsbruck Medical University, Innsbruck, Austria

*** Corresponding authors**

Dr Atbin Djamshidian

Department of Neurology
Medical University of Innsbruck
Anichstrasse 35, 6020 Innsbruck, Austria.
Tel: +43 512 504 23850; Fax: +43 512 504 23852
E-mail: atbin.djamshidian-tehrani@i-med.ac.at

Prof Thomas T Warner

Reta Lila Weston Institute of Neurological Studies, Institute of Neurology, University College London
The National Hospital for Neurology and Neurosurgery, Queen Square, London, UK
1 Wakefield Street, WC1N1PJ, London, United Kingdom
Telephone: +44 02076794246 / Email: t.warner@ucl.ac.uk

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ABSTRACT

Fifteen individuals with Parkinson's disease (PD) and impulsive compulsive behaviours (PD+ICB) were compared to 15 PD patients without ICBs (PD-ICB) and 15 healthy controls (HC) on a pro-saccades and an anti-saccades task to assess if ICBs are associated with distinct saccadic abnormalities. PD+ICB made shorter saccades than HC and more direction errors in the anti-saccades task than PD-ICB and HC, suggesting that patients with ICBs have greater difficulty in suppressing automatic saccades towards a given target. Saccadic assessment has the potential to evolve into a marker to guide therapeutic decisions in patients at risk of developing ICBs.

INTRODUCTION

The motor abnormalities in PD are frequently reflected in saccadic movement in the form of hypometria and increased reaction time (latency).[1, 2] While automatic saccades appear to be preserved in PD,[3] voluntary saccades are impaired.[4-6] Although treatment with levodopa can improve some of these abnormalities,[5] anti-saccadic reaction time and direction errors worsen as PD progresses.

Impulsive compulsive behaviours (ICBs) such as the dopaminergic dysregulation syndrome, hypersexuality, pathological gambling, compulsive shopping and punding, affect 16% of patients with PD.[7] Anti-saccadic error rate has been associated with impulsivity in healthy controls (HC),[8] but to date no studies have assessed eye movements of individuals with PD and ICBs (PD+ICB). The presence of motor and reflection impulsivity in PD+ICB[9] would predict that premature saccades and anti-saccade direction errors are increased in these individuals. To answer this question, we studied pro and anti-saccades of PD+ICB and compared the results with individuals with PD without ICBs (PD-ICB) and HC.

ICBs are usually underreported by PD patients[10] and distinct saccadic abnormalities in PD+ICB may represent a novel way of identifying these behavioural abnormalities, which would be of clinical value.

MATERIAL AND METHODS

Fifteen PD+ICB were matched with 15 PD-ICBs and 15 HC. Diagnosis of ICBs was based on the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale (QUIP-RS)[11] and confirmed with an interview. Patients with Montreal Cognitive Assessment (MoCA) score < 26 were excluded. For details on other scales/questionnaires used see supplementary materials. PD patients using levodopa were tested one hour after intake. Eyetracking was conducted with an e(ye)BRAIN©T2 device (SuriCog©). The research was approved by the local ethics committee. Two paradigms were created:

. **Pro-saccade task**.

Participants started focusing on a central grey dot and made a saccade to a blue dot appearing eccentrically (15 degrees horizontally) on the screen, displayed for 1500 milliseconds.

. **Anti-saccade task**.

Participants were instructed to focus on a central grey dot. Immediately after it disappeared, a red dot appeared randomly on either side of the screen 15 degrees horizontally. Participants were instructed to look to the opposite side of the screen and return their eyes to the central fixation point after the red dot disappeared, 1500 millseconds later.

Forty randomized trials were conducted to each side, totalling 80 trials. Direction errors, saccadic movements towards the opposite direction of the visual stimulus, were computed as total values and proportion of errors in relation to the total number of detected saccades. Data points outside the interquartile ranges were excluded. Due to the possibility that saccades with latency > 900ms or < 120ms were not related to stimulus presentation, these were excluded from the analysis.

Saccadic parameteres were corrected for multiple comparisons using the Benjamini-Hochberg[12] method. A p value < 0.05 was considered significant. For statistical analysis details see supplementary materials.

RESULTS

There were more males in the PD+ICB (87%) and PD-ICB (80%) groups compared with HCs (47%). PD+ICB scored higher on the QUIP-RS, AIMS and UPDRS III. None of PD+ICB were receiving drugs for ICBs and no PD patients were using anticholinergics. For demographic/clinical data see table 1, for types of ICBs see supplementary materials.

Table 1 – Demographic and clinical characteristics divided by group

	PD+ICBs	PD-ICBs	HC	p value
N	15	15	15	
Females	2 (13.3%)	3 (20%)	8 (53.3%)	**0.035***
Age in years (SD)	53.6 (± 9.8)	54.6 (± 7.3)	53 (± 9.1)	0.880λ
Average age at PD onset in years (SD)	42.7 (± 10.3)	45.9 (± 7.5)	-	0.344‡
Average PD duration in years (SD)	11.1 (± 4.3)	8.7 (± 4.5)	-	0.152‡
Current use of DA	9 (60%)	9 (60%)		1.000*
Total DA LEDD (N = 9) (SD)	164.7 (± 133.3)	242.4 (± 96.6)	-	0.178‡
Current use of MAOi	3 (20%)	1 (6.66%)		0.330β
Levodopa daily dose in mg (SD)	743.6 (± 317.6)	605.7 (± 405.7)		0.309‡
Total LEDD (SD)	895.8 (± 397.5)	744.5 (± 466.2)	-	0.347‡
Hoehn & Yahr	1: 0 2: 15	1: 3 2: 12	-	0.224β
QUIP-RS (SD)	39.9 (± 11.1)	10.07 (± 7.4)	-	**<0.001λ**
AIMS (SD)	7.4 (± 4.6)	2.87 (± 3.3)	-	**0.005λ**
UPDRS III (SD)	24.6 (± 6.9)	13.73 (± 5.6)	-	**<0.001λ**
MoCA (median, IQR)	28 (27; 29)	29 (27; 30)	28 (27; 29.7)	0.533φ
FAB (median, IQR)	17.5 (16; 18)	18 (17; 18)	18 (18; 18)	0.089φ

Demographic and clinical characteristics divided by group. SD – standard deviation; PD – Parkinson's disease; DA – dopamine agonist; LEDD – levodopa equivalent daily dose; MAOI – monoamine oxidase inhibitor; QUIP-RS - Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale; UPDRS III - Unified Parkinson's Disease Rating Scale part III; AIMS - Abnormal Involuntary Movements Scale; MoCA - Montreal Cognitive Assessment; FAB - Frontal Assessment Battery; Ms – milliseconds; IQR – interquartile range.. *Chi-square test; λ ANOVA; ‡ Independent samples t-test; φ Kruskal-Wallis test; β Fisher's exact test. Significant results in bold. Results expressed in mean values and standard deviation and total values and proportions.

The number of outlying data points excluded and premature saccades was similar between groups in both tasks. We found no difference between centripetal and centrifugal saccadic amplitudes in the pro-saccade task, and no differences in saccadic errors in the anti-saccade task between centripetal and centrifugal saccades, across all groups. As centripetal saccades are more influenced by visual determinants[13], we henceforth report centrifugal saccade data only. There were no differences in the latency or amplitude of pro-saccades, nor anti-saccadic latency between groups. Anti-saccade amplitude was similar between groups (table 2), but a post-hoc analysis showed decreased amplitude in PD+ICB compared to HC (p = 0.021, Mann-Whitney), but no difference between PD+ICB and PD-ICB (p = 0.110) or between PD-ICBs and HC (p = 0.097).

Anti-saccadic error rate differed between groups (table 2). Post-hoc analysis revealed that PD+ICB made more errors than PD-ICB (p = 0.006) and HC (p = 0.001), but there was no difference between PD-ICB and HC (p = 0.802). Anti-saccadic reaction time for accurate saccades and direction errors are found in supplementary materials.

We also analysed fixation data as this is relevant to interpretation of saccadic function. The number and duration of fixation deviations from the target (fixation instability) were greater in PD+ICB compared to PD-ICB, but this was not statistically significant (p>0.1). There were no correlations between fixation instability and anti-saccadic errors, age, disease duration, UPDRSIII, AIMS or QUIP-RS.

Table 2 – Results of the pro-saccades and anti-saccades tasks

	PD+ICBs	PD-ICBs	HC	p value
N	15	15	15	
Pro-saccades task				
Total saccades (mean, SD)	73.2 (76; 13)	75.8 (78; 5)	73.8 (78; 8)	0.195 φ
Latency in ms (median, IQR)	299.9 (246.7; 316.2)	271.9 (246.2; 289.4)	264.6 (250.4; 302.5)	0.537 φ
Amplitude (°)	14.8 (± 2.2)	15.1 (± 2.6)	16.1 (± 2.3)	0.537 λ
Premature saccades (median, IQR)	9 (4; 13)	8 (2; 12)	7 (2; 10)	0.545 φ
Anti-saccades task				
Total saccades (mean, SD)	77.4 (78; 5)	76.8 (79; 3)	78 (80; 2)	0.122 φ
Latency in ms (median, IQR)	318.6 (308.6; 359.5)	300.2 (281.2; 378.6)	326.4 (285.5; 345.4)	0.315 φ
Amplitude in° (median, IQR)	13.5 (12; 15)	15.5 (13.8; 16.9)	16.8 (15.7; 18.5)	0.07φ
Direction errors (SD)	31.1 (± 13.1)	18.9 (± 12)	15.2 (± 13.9)	**0.015** λ
Direction errors % (SD)	48.6 (± 22)	25.2 (± 16.8)	20.7 (± 19.5)	**0.006** λ
Premature saccades (median, IQR)	1 (0; 1)	0 (0; 2)	0 (0; 1)	0.315 φ

Eye movements characteristics divided by group. Direction errors are displayed as average number of direction errors per group (N) and as proportion of direction errors in relation to the total number of detected saccades (%). SD - standard deviation; PD – Parkinson's disease; ms – milliseconds. λ ANOVA; φ Kruskal-Wallis test; Significant results in bold. Benjamini Hochberg correction for multiple comparisons used for all results. Results expressed in mean values and standard deviation (SD) for variables with normal distribution or mean values and median and interquartile range (IQR) for variables with non-normal distribution.

DISCUSSION

This is the first study of saccades in PD+ICB. Corroborating previous findings showing preserved automatic saccades in PD,[3-6] ICB does not influence pro-saccadic behaviour. The superior colliculus (SC) is the point of convergence for cortical and subcortical structures that influence saccadic control[1] and is modulated by the basal ganglia.[14] This structure is under tonic inhibiton from the substantia nigra pars reticulata (SNr). Cortical visual signals are initially directed to the caudate,

which connects to the SNr via direct and indirect pathways. The former inhibits the SNr and release the SC to perform a saccade, whereas the latter increases SC inhibition preventing the generation of saccades towards 'valueless' objects.[14, 15] The SNr is affected later in PD,[16] therefore integrity of such pathways in early PD could explain the preservation of pro-saccades. It is unlikely that dopaminergic medication contributed to this as levodopa slows reaction time of pro-saccades.[5, 17] However, it is possible that the sample size was insufficient to detect subtle differences.

Contradictory data on anti-saccadic reaction time in PD has been published.[3] Here, all patients were were tested during ON which may explain the lack of differences in anti-saccadic latencies. The amplitude of anti-saccades, however, was lower in PD+ICB compared to HC. We were unable to replicate findings of previous reports which found that PD-ICB have hypometric saccades.[3] As previously described in a PD population, saccadic hypometria is unaffected by levodopa use.[5]

More premature saccades were made in the pro-saccades than the anti-saccades task. It has been shown that anticipatory saccadic movements can occur with predictable tasks similar to our pro-saccade paradigm.[18] Increased anti-saccadic error rate has been reported in drug-naïve PD,[19] but the error rate found here was higher than previously reported, possibly due different assessment protocols. Whereas PD+ICB made more direction errors than both groups, there were no differences between PD-ICB and HC. This is unlikely to be related to abnormalities of fixation, given similar rates of fixation instability across both groups.

PD+ICBs have reflection impulsivity, temporal discounting and a bias towards risky choices in decision-making tasks.[9] However, considering the short time between target onset and saccadic movement and the low number of premature saccades, it is unlikely that decision-making abnormalities are behind the higher error rate in PD+ICB. Previous studies show that correct performance in the anti-saccadic task requires top-down inhibition of neurons in the SC before target onset.[1] PD-related dopaminergic depletion in the dorsolateral prefrontal cortex coupled with deficits in cortical inhibitory circuits in PD+ICB[20] may explain the failure to suppress an automatic saccade.[21]

An important caveat is that PD+ICB had higher UPDRS scores, which could contribute to increased anti-saccadic error rate; both anti-saccadic error rate and reaction time increase as PD progresses.[22, 23] However, there are important differences between our study and previous reports of saccadic abnormalities in advanced PD. Firstly, in our study PD+ICB exhibited a significantly higher error rate (48.62%) compared to the literature (36.2%).[23] Secondly, in our study the anti-saccadic reaction time was also shorter (318.6ms) than a previous report (410ms).[23] Thirdly, severity of bradykinesia has been correlated with longer anti-saccadic latencies[23] but we have found no differences in reaction time between PD+ICB and PD-ICB. Lastly, direction errors were not correlated with QUIP-RS, AIMS nor UPDRS scores. Therefore, although the UPDRSIII suggests that PD+ICB have more advanced PD, the anti-saccades data do not corroborate this. Although the UPDRSIII score influences performance in PD-ICB[23] it is likely that cognitive impulsivity is contributing to poor performance in PD+ICB.

One limitation of this study is the small sample size. This was addressed by sampling 80 saccades in each task, ensuring patients were offered breaks between tasks to avoid fatigue. There were more

female HC; previous data show that saccadic parameters do not differ between sexes,[24] although one study reported a higher anti-saccadic error rate in women compared to men.[25] However, the 20% error rate of HC in our study is lower than the findings of that study.

This is the first study of saccades in PD+ICBs, who made hypometric anti-saccades and a higher number of anti-saccade direction errors. This finding may have important clinical implications if antisaccadic error rate could be confirmed as a marker for ICBs. Future studies should investigate whether PD+ICB are less able to inhibit saccades to less salient stimuli. Tasks with short preparation times, or which present sensory information before motor choice, could help understanding decision-making in such a short time frame and the health of the frontal inhibitory circuits modulating it.[26, 27]

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Author's roles

PB: conception, organization and execution of the research project; statistical analysis design and execution; writing of the first draft, review and final approval the manuscript.

DK: review and critique of the statistical analysis; review, critique and final approval of the manuscript.

AJL: review and critique of the statistical analysis; review, critique and final approval of the manuscript.

AD: conception and organization of the research project; design, review and critique of the statistical analysis; review, critique and final approval of the manuscript.

TTW: conception and organization of the research project; design, review and critique of the statistical analysis; review, critique and final approval of the manuscript.

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PB has nothing to disclose.
DK has nothing to disclose.
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TTW has nothing to disclose.

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Supplementary Material - Saccadic direction errors are associated with impulsive compulsive behaviours in Parkinson's disease patients.

Methodology

All PD patients fulfilled the Queen Square Brain Bank diagnostic criteria.[1]

The diagnosis of ICBs was made based on the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale (QUIP-RS) scores using previously published cutoff values[2] and confirmed with a semi-structured interview.

All participants were assessed with the following questionnaires and scales: the MoCA and the Frontal Assessment Battery (FAB). Patients were also assessed with the QUIP-RS, the Unified Parkinson's Disease Rating Scale (UPDRS) part III and the Abnormal Involuntary Movements Scale (AIMS).

To ensure PD patients were tested in the ON state, patients on levodopa were assessed one hour after taking levodopa. Eye movements assessments were carried out with an e(ye) BRAIN© T2 device. Before each task a twelve-point calibration of the eyetracker infrared cameras and automated calibration of the head sensor were conducted.

. **Pro-saccades task details**.

Participants started by focusing on a grey dot measuring 0.32 degrees of visual angle on the centre of the screen. They were then instructed to make a saccade to a blue dot appearing eccentrically (15 degrees from centre) on the screen, displayed for 1500 milliseconds (ms). The central grey dot remained on display throughout the assessment. After 1500 ms, the blue dot disappeared and patients had to return their eyes to the central fixation dot.

. **Anti-saccades task details.**

Participants were instructed to focus on a central grey dot measuring 0.32 degrees of visual angle that was displayed for 1500 ms. In this task a step paradigm was used. Immediately after the grey dot disappeared, without delay, a red dot appeared randomly on either side of the screen 15 degrees away from the centre.

Data analysis was conducted initially with the e(ye) BRAIN software me(ye) analysis©. The computer was programmed to identify the first saccadic movement occurring after the target appeared that exceeded a speed of 30 degrees per second. The quality of the recording from both eyes was inspected visually by one of the authors (PB), and the channel with best recording chosen for data analysis. A poor quality signal was identified when there was too much interference to prevent accurate detection of saccades and/or when the computer failed to identify more than 75% of the expected saccadic movements, in both cases recordings were excluded from analysis. Latency and gain were calculated for each detected saccade and mean values used for comparison.

Considering that normal subjects generate a saccade within approximately 200 ms,[3] saccades with latencies between 120 and 180 ms were classified as premature and included in the analysis. Saccadic amplitude was calculated as average of all saccades. The number of direction errors in the anti-saccades task was calculated for each participant and mean values used for comparison. Parametric data was compared using independent samples t-test and ANOVA and non-parametric Kruskal-Wallis. Mann-Whitney U test and Wilcoxon matched pairs were used for post hoc comparison of saccadic parameters. Proportions were compared with the chi-square test, except if expected cell count was less than 5 when Fisher's exact test was used

Results

Six patients with PD were excluded: two because of low MoCA scores, three because of poor quality of recording and one because of a technical fault with the computer processing unit. One healthy individual was excluded because of poor quality of the recording. Fifteen patients were included in each group: patients with PD and ICBs (PD+ICBs), patients with PD without ICBs (PD-ICBs) and healthy controls (HC). An example of raw data is displayed in figures 1 and 2.

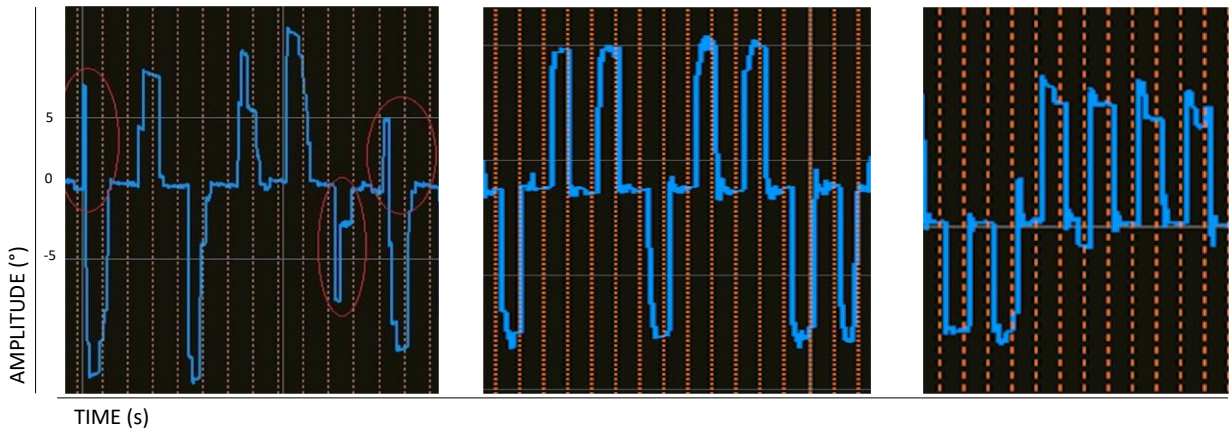

Figure 1. Raw data of one patient with ICB (left image), one patient without ICB (middle image) and one healthy individual (right image). PD+ICB made a significantly higher number of direction errors (red circles). X axis represents time and y axis amplitude.

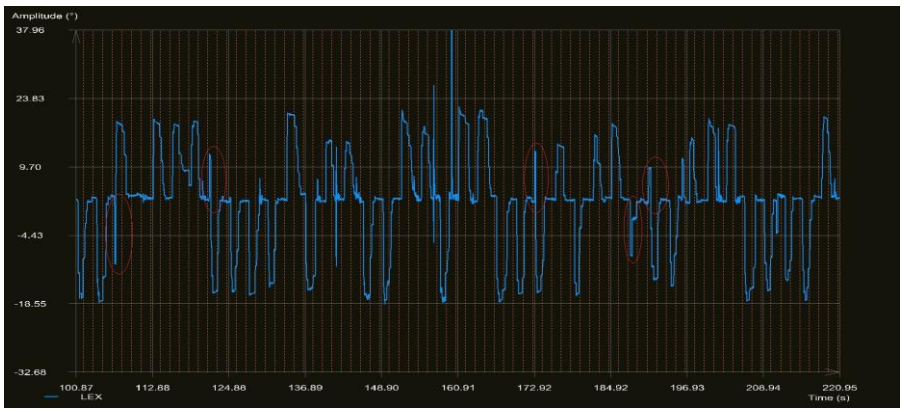

Figure 2. Raw data of one patient with ICB showing direction errors (red circles) and X axis represents time and y axis amplitude.

In the PD+ICB group 5 patients had a single ICB (2 compulsive sexual behaviour (CSB), 2 punding/hobbyism (Pu) and 1 compulsive shopping) (CS) and 10 multiple ICBs (2 CSB with compulsive eating (CE), 1 CSB with pathological gambling (PG), 1 Pu with CS, 2 Pu with CE, 1 CSB with CS, 1 CSB with CS and CE, 1 with CS, CE and Pu, and 1 with PG, CS and HP.

Anti-saccades that generated a direction error had shorter reaction times as seen in figure 3.

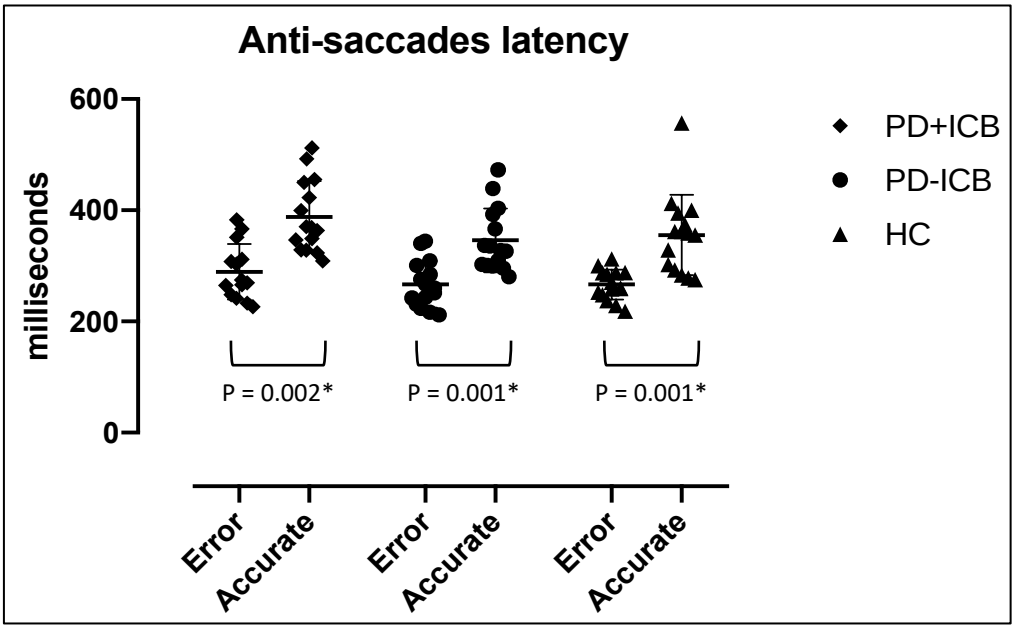

Figure 3. Latency of anti-saccades that were accurate and that were associated with a direction error. No differences between groups were observed. Within group comparison revealed shorter reaction times of saccades that were associated with a direction error. *Wilcoxon matched pairs.

References

1. Munoz DP, Everling S. Look away: the anti-saccade task and the voluntary control of eye movement. Nat Rev Neurosci 2004;5(3):218-228.
2. Matsumoto H, Terao Y, Furubayashi T, et al. Small saccades restrict visual scanning area in Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society 2011;26(9):1619-1626.
3. Briand KA, Strallow D, Hening W, Poizner H, Sereno AB. Control of voluntary and reflexive saccades in Parkinson's disease. Exp Brain Res 1999;129(1):38-48.
4. Chan F, Armstrong IT, Pari G, Riopelle RJ, Munoz DP. Deficits in saccadic eye-movement control in Parkinson's disease. Neuropsychologia 2005;43(5):784-796.
5. Hood AJ, Amador SC, Cain AE, et al. Levodopa slows prosaccades and improves antisaccades: an eye movement study in Parkinson's disease. J Neurol Neurosurg Psychiatry 2007;78(6):565-570.
6. Chambers JM, Prescott TJ. Response times for visually guided saccades in persons with Parkinson's disease: a meta-analytic review. Neuropsychologia 2010;48(4):887-899.
7. Weintraub D, Koester J, Potenza MN, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. Archives of neurology 2010;67(5):589-595.
8. Spinella M. Neurobehavioral correlates of impulsivity: evidence of prefrontal involvement. Int J Neurosci 2004;114(1):95-104.
9. Averbeck BB, O'Sullivan SS, Djamshidian A. Impulsive and compulsive behaviors in Parkinson's disease. Annual review of clinical psychology 2014;10:553-580.
10. Perez-Lloret S, Rey MV, Fabre N, et al. Do Parkinson's disease patients disclose their adverse events spontaneously? Eur J Clin Pharmacol 2012;68(5):857-865.
11. Weintraub D, Mamikonyan E, Papay K, Shea JA, Xie SX, Siderowf A. Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale. Movement disorders : official journal of the Movement Disorder Society 2012;27(2):242-247.
12. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. Journal of the Royal Statistical Society Series B (Methodological) 1995;57(1):289-300.
13. Camors D, Trotter Y, Pouget P, Gilardeau S, Durand JB. Visual straight-ahead preference in saccadic eye movements. Sci Rep 2016;6:23124.
14. Hikosaka O, Kim HF, Yasuda M, Yamamoto S. Basal ganglia circuits for reward value-guided behavior. Annu Rev Neurosci 2014;37:289-306.
15. Kim HF, Amita H, Hikosaka O. Indirect Pathway of Caudal Basal Ganglia for Rejection of Valueless Visual Objects. Neuron 2017;94(4):920-930.e923.
16. Jellinger K. Neurodegeneration: The Molecular Pathology of Dementia and Movement Disorders: International Society of Neuropathology. Blackwell Publishing Ltd, 2011.
17. Michell AW, Xu Z, Fritz D, et al. Saccadic latency distributions in Parkinson's disease and the effects of L-dopa. Exp Brain Res 2006;174(1):7-18.
18. Holmqvist K, Nyström M, Andersson R, Dewhurst R, Jarodzka H, van de Weijer J. Eye Tracking: A comprehensive guide to methods and measures2011.
19. Antoniades CA, Demeyere N, Kennard C, Humphreys GW, Hu MT. Antisaccades and executive dysfunction in early drug-naive Parkinson's disease: The discovery study. Movement disorders : official journal of the Movement Disorder Society 2015;30(6):843-847.
20. Djamshidian A, Averbeck BB, Lees AJ, O'Sullivan SS. Clinical aspects of impulsive compulsive behaviours in Parkinson's disease. Journal of the neurological sciences 2011;310(1-2):183-188.
21. Pretegiani E, Optican LM. Eye Movements in Parkinson's Disease and Inherited Parkinsonian Syndromes. Front Neurol 2017;8:592.
22. Terao Y, Fukuda H, Yugeta A, et al. Initiation and inhibitory control of saccades with the progression of Parkinson's disease - changes in three major drives converging on the superior colliculus. Neuropsychologia 2011;49(7):1794-1806.
23. Kitagawa M, Fukushima J, Tashiro K. Relationship between antisaccades and the clinical symptoms in Parkinson's disease. Neurology 1994;44(12):2285-2289.

24. Wilson SJ, Glue P, Ball D, Nutt DJ. Saccadic eye movement parameters in normal subjects. Electroencephalography and clinical neurophysiology 1993;86(1):69-74.
25. Li Q, Amlung MT, Valtcheva M, et al. Evidence from cluster analysis for differentiation of antisaccade performance groups based on speed/accuracy trade-offs. International journal of psychophysiology : official journal of the International Organization of Psychophysiology 2012;85(2):274-277.
26. Haith AM, Huberdeau DM, Krakauer JW. The influence of movement preparation time on the expression of visuomotor learning and savings. J Neurosci 2015;35(13):5109-5117.
27. Stanford TR, Shankar S, Massoglia DP, Costello MG, Salinas E. Perceptual decision making in less than 30 milliseconds. Nat Neurosci 2010;13(3):379-385.
28. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55(3):181-184.
29. Kveraga K, Boucher L, Hughes HC. Saccades operate in violation of Hick's law. Exp Brain Res 2002;146(3):307-314.