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The effect of levodopa on saccades – Oxford Quantification in Parkinsonism study

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ABSTRACT

Objectives: The evaluation of novel disease modifying drugs requires biomarkers that are simultaneously sensitive to disease state but resistant to the effects of background symptomatic treatment. Saccadic eye movement parameters have been proposed as a neurophysiological biomarker for Parkinson's disease (PD) and so it is important to know how they are affected by dopaminergic medication. Studies to date are conflicting: some have concluded that medication prolongs saccadic latencies while others suggest they are shortened. We aimed to characterise the effects of antiparkinsonian medication on prosaccadic and antisaccadic parameters in a large cohort of PD patients and age matched healthy controls and to survey the current literature in comparison to the study findings.

Methods: We studied saccades both off and on medication in 38 PD patients and 34 healthy controls (HC). Latencies, amplitudes, velocities, and directional errors were evaluated, using a published standardised protocol. We then combined this study and previously published literature in a meta-analysis of the effects of antiparkinsonian medication on prosaccadic latency (PSL).

Results: PSL is significantly prolonged by dopaminergic medication in PD, from a mean of 222.7 ms in the OFF medication state to a mean of 236.0 ms in the ON medication state ($p = 0.028$). This effect size is comparable to the difference between PD OFF medication and healthy control values. There was no statistically significant change in any other saccadic parameter with medication. Of particular note, antisaccadic latency was almost exactly the same on and off medication (means of 414.9 ms and 417.2 ms respectively, $p = 0.97$), while being almost 20% longer in PD patients compared to healthy controls (HC mean 357.2 ms; PD ON vs HC $p = 0.015$; PD OFF vs HC $p = 0.0066$).

Conclusion: PSL is significantly affected by dopaminergic medication which may complicate its use as a biomarker in drug trials. Antisaccadic latency is particularly interesting in this regard because it shows a large disease effect with no medication effect.

1. Introduction

The aim of the OxQUIP (Oxford Quantification in Parkinsonism) study is the identification and validation of novel neurophysiological and cognitive biomarkers for parkinsonian disorders, that have the potential to provide quantitative measures of disease state, supplanting the present means of clinical evaluation using rating scales. The major motivation for this work is to provide tools which can enable more rapid evaluation of novel therapeutics in clinical trials.

One potential source of biomarkers that we have been investigating is saccadic eye movements. Oculomotor control circuits pass through many of the same parts of the basal ganglia as their somatic counterparts, and eye movement parameters are known to be abnormal in Parkinson's disease (PD) [1–4]. Saccades have been investigated in several studies as potential neurophysiological biomarkers for PD [5–8]. They are stereotyped movements that are easy to elicit, they can be measured accurately and objectively with the appropriate equipment, large numbers of data points can be gathered quickly, and longitudinal studies are not confounded by a learning effect. A suitable choice of the particular measure permits a wide dynamic range of

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measurement, for example antisaccadic parameters are abnormal even in newly diagnosed patients, where other scores may lack sensitivity or suffer from floor effects [7].

Combinations of saccadic tasks permit evaluation of different aspects of the function of cortico-basal ganglia circuits. A prosaccadic task – looking towards a visual stimulus – usually represents function purely within the oculomotor loop. More complex ones such as the antisaccadic task - looking *away* from a visual stimulus - [9] involve inhibition of the normal reflexive response, which is known to require the dorsolateral prefrontal cortex (DLPFC), part of the prefrontal loop [10–12].

One of the most important potential uses for a biomarker is in the appraisal of candidate drugs in clinical trials. To place measurements in context, it is critical to understand the effects of existing antiparkinsonian medication on saccadic eye movements. Previous studies examining this have produced conflicting results [13] where changes in saccadic parameters have differed not only in degree, but in some cases also in direction. For example, levodopa has been reported as both increasing [14–18] and decreasing [19–21] prosaccadic latency. Other reported effects include a reduction in the antisaccadic error rate [22], and improvement of prosaccadic accuracies [23] and amplitudes [24].

We report here one of the largest studies of the effects of antiparkinsonian medication on saccades, and perform a meta-analysis incorporating this and pre-existing studies.

2. Materials and methods

2.1. Subjects

The work presented here was part of the OxQUIP study, which was conducted in the John Radcliffe Hospital in Oxford and was approved by the ethics committee (REC reference 16/SW/0262). The OxQUIP study is a large prospective cohort study of neurophysiological biomarkers in parkinsonian patients. Written informed consent was obtained from all participants after the procedures were explained to them.

38 PD patients and 34 age-matched healthy controls took part (see Table 1). The healthy controls had no history of neurological or psychiatric disorders and were not taking any medication at the time of testing.

Patients had clinically probable idiopathic PD and the UK PD brain bank criteria were used to determine this [25].

Patients were asked to omit their antiparkinsonian medication on the morning of testing. We tested them twice, once when they arrived (off meds), then they were asked to take their medication and we tested them a second time 60 min later. Testing Parkinson's patients on and off medication in this way has been extensively performed in research studies, without any reported detrimental effects [26,27].

2.2. Saccadic paradigm

Visually guided horizontal saccadic eye movements were recorded using an infra red head-mounted oculometer, with three built in lasers projecting red spots in a horizontal line on a plain matt surface. The lateral targets were ± 10° from the central one. We used a previously described protocol [28] consisting of five blocks as follows: 60 prosaccades, three blocks of 40 antisaccades, and a final block of 60 prosaccades. All blocks were preceded by an initial calibration set consisting of 12 prosaccades (6 to the right and 6 to the left). The paradigm takes approximately 10–15 min.

For both prosaccades and antisaccades a central fixation target was displayed for a random foreperiod of 1.0–2.0 s. Then one of the peripheral targets chosen randomly either to the left or right was presented, and the central stimulus simultaneously removed. The peripheral target remained illuminated until 200 ms after the end of the ensuing saccade. For the prosaccadic blocks, participants were instructed to make a saccade as quickly as possible to the new target position. For the antisaccadic ones, participants were instructed to make a saccade in the opposite direction.

Table 1
Demographics, clinical characteristics and rating scores in the PD and HC groups.

	PD (n = 38) Mean (range)	HC (n = 34) Mean (range)	p value
Age, yrs	65.1 (47-80)	65.2 (51-78)	0.97 [a]
Sex, Male/Female	23/15	15/19	0.24 [b]
Dominant Hand, Right/All	37/38	27/34	0.052 [b]
Disease duration, yrs	2.9 (0.42-7)	NA	
LED, daily, mg	507 (200–1147.5)	NA	
taken at the visit, mg	207 (100-520)		
Years of education, yrs	15.8 (12-20)	15.4 (12-20)	0.53 [c]
BMI, kg/m^2	26.3 (17.8–39.0)	25.8 (20.7–36.3)	0.61 [a]
Motor assessment			
HY scale, OFF (number of patients by stage)	Stage 1–15 Stage 2–21 Stage 3–2	0	
HY scale, ON (number of patients by stage)	Stage 1–17 Stage 2–19 Stage 3–2		
MDS-UPDRS III, OFF	25.0 (5-54)	4.4 (0-25)	
ON	17.7 (0-49)		
Neuropsychological tests, on state			
MMSE	29.0 (25-30)	29.0 (25-30)	0.44 [c]
MOCA	27.3 (19-30)	27.3 (24-30)	0.67 [c]
Phonemic fluency	46.1 (14-69)	47.1 (27-85)	0.75 [a]
Semantic fluency	41.7 (21-73)	41.7 (26-71)	0.92 [c]

PD, Parkinson's Disease; HC, Healthy control; LED, levodopa equivalent dose; BMI, body mass index; HY, Hoehn and Yahr stage; MDS-UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale; MMSE, Mini-Mental State Examination; MOCA, Montreal Cognitive Assessment; NA, not applicable.
[a] independent *t*-test; [b] Chi-square test; [c] Mann Whitney *U* test.

2.3. Data and statistical analysis

Raw data from the saccadometer were downloaded onto our lab computer with the LatencyMeter software (Ober Consulting, version 6.10). For each subject, saccadic data were analysed using LatencyMeter; this software determines the saccadic latency using a saccade-detection algorithm based on velocity and acceleration. During pre-processing this software and integrated hardware automatically accounts for eye blinks and head movements. For each participant we then calculated mean latency (time taken from stimulus appearance to onset of the resulting saccade), saccade amplitude, and peak saccadic velocities for both prosaccades and antisaccades, as well as antisaccadic error rate (AER). AER was defined as the percentage of directional errors, i.e. saccades triggered towards the lateral target instead of away from it. Saccades with latencies less than 80 ms or over 1000 ms were excluded from the analysis (this represented < 1% of all saccades).

Data were tested for normality using a Shapiro-Wilk test. Normally distributed data were compared using a *t*-test (paired or unpaired as required) while non-normal data were compared using a Mann-Whitney *U* test (for unpaired data) or Wilcoxon signed rank test (for paired data). Proportions were compared using a Chi Square test. The test used in each case is indicated in Tables 1 and 2.

2.4. Meta-analysis

A meta-analysis was performed using data from published studies describing the influence of medication on prosaccadic latency, together with similar data from this study. Suitable studies for inclusion were identified by using the terms: (“eye movement” OR “ocular motor” OR “ocular movement” OR “oculomotor” OR “visual movement” OR *saccade* OR “orienting” OR “attention”) AND (“Parkinson” OR

Table 2
Saccadic parameters.

	L-dopa treated PD patients		*p* value	HC Mean (range)	*p* value OFF vs HC, ON vs HC
	OFF Mean (range)	ON Mean (range)			
Prosaccade					
Latency, ms	222.7 (172-281)	236.0 (152-363)	0.028	203.7 (144-290)	0.018, 0.0022
Amplitude, deg	9.9 (8.9–10.6)	9.9 (9.2–11.6)	0.91	10.0 (9.3–11.2)	0.41, 0.34
Peak velocity, deg/s	390.8 (285-531)	378.4 (230-583)	0.075	367.7 (284-513)	0.054, 0.38
Antisaccade					
Latency, ms	414.9 (268-764)	417.2 (270-696)	0.97[a]	357.2 (207-677)	0.0066, 0.015
Amplitude, deg	10.6 (5.2–15.2)	11.0 (5.9–17.9)	0.32[a]	11.1 (8.1–15.2)	0.28, 0.89
Peak velocity, deg/s	353.8 (185-570)	336.1 (171-533)	0.092	333.2 (213-451)	0.33, 0.95
AER, %	56.1 (0.8–91.7)	57.2 (0.8–93.8)	0.63	43.2 (11.7–88.3)	0.039, 0.029

PD, Parkinson's Disease; HC, Healthy control; AER, antisaccadic error rate. Superscript [a] indicates that a Wilcoxon signed rank test was used; all tests not marked in this way were t-tests.

"Parkinsonism") AND ("levodopa" OR "dopamine" OR "dopamine agonist ") of Medline, PubMed, Web of Science and Google scholar databases for original articles (review, patent, case report excluded) published up to 2018. This initial search yielded 395 results. Following deduplication, 262 remained. We then screened the title and abstract of these studies, of which 40 were deemed relevant and therefore selected for full text review. Out of these 40 studies we excluded articles not providing detailed information on the subjects included, the medication challenge, the eye movement recording procedure, or the results of the eye movement recordings. At the end of this screening process, 10 studies plus OxQUIP were included in the meta-analysis, of which 7 studies reported results with only levodopa-treated patients.

The meta-analysis was performed twice. The first run was limited to studies involving only levodopa. The second analysis incorporated all studies including those where patients were on additional anti-parkinsonian medications such as dopamine agonists. In the first analysis we included 17 patients from this study who were on levodopa treatment only, and in the second analysis we included all 38 patients reported here.

The meta-analysis was performed using Review Manager v5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014), with a random-effect model. For each study, we extracted the mean and the standard deviation (SD) of the prosaccadic latency of the PD patients, both on and off medications. Effect sizes are described in mean milliseconds together with their 95% confidence intervals. The heterogeneity (Q) and inconsistency (I^2) across studies were calculated. The Z score was used to test for overall effect and the Chi-square statistic to assess heterogeneity; both tests using an alpha level of 0.05.

3. Results

3.1. OxQUIP data analysis

The demographic details, clinical characteristics and rating scores for both the PD and HC groups are shown in Table 1. 17 PD patients were on levodopa only; 7 patients were on levodopa plus a dopamine agonist; 9 were on levodopa plus a monoamine oxidase B inhibitor; and 5 patients were on a combination of three or more medication types. As expected, in the PD group the UPDRS motor score significantly improved after taking levodopa ($p < 0.0001$). There was no significant change in the HY scale ($p = 0.32$). At the time of testing, the patients did not exhibit signs of cognitive impairment (MMSE and MOCA data to support this are given in Table 1).

Fig. 1 shows the measured saccadic parameters for all participants, with each point representing the mean value across all trials for an individual. Group means are given in Table 2. Prosaccadic latency (PSL, Fig. 1A) differed significantly between the on and off medication states in the PD group (means of 236.0 ms and 222.7 ms respectively, $p = 0.028$), and between PD patients in either state and healthy controls (HC mean 203.7 ms; PD ON vs HC $p = 0.0022$; PD OFF vs HC $p = 0.018$). By contrast, prosaccadic amplitude (PSA, Fig. 1C) and prosaccadic peak velocity (PSPV, Fig. 1E) were unaffected by medication state or the presence of disease.

The antisaccadic latency (ASL, Fig. 1B) was nearly identical on and off medication in the PD group (means of 414.9 ms and 417.2 ms respectively, $p = 0.97$). There was however a substantial difference between PD and HC patients (HC mean 357.2 ms; PD ON vs HC $p = 0.015$; PD OFF vs HC $p = 0.0066$). As with prosaccades, antisaccadic amplitude (ASA, Fig. 1D) and antisaccadic peak velocity (ASPV, Fig. 1F) were unaffected by medication or disease. Antisaccadic error rate (AER, Fig. 1H) was also not significantly affected by medication (PD ON mean 57.2%, PD OFF mean 56.1%, $p = 0.63$), but differed significantly between PD patients and HC (HC mean 43.2%; PD ON vs HC $p = 0.029$; PD OFF vs HC $p = 0.039$).

3.2. Meta-analysis of prosaccadic latency shifts

We meta-analysed the effects on PSL seen in this study together with those from the published literature. This analysis was performed twice. First we analysed the effect on PSL seen in studies where the medication challenge was levodopa only with no other dopaminergic medication present (Fig. 2A). Most of the existing published studies with sufficient data to contribute to the meta-analysis (7 of 10 studies excluding ours) concerned patients challenged with levodopa only. We therefore felt that for the purposes of optimum comparability we should report this subgroup of our patients by itself and meta-analyse it together with those 7 studies. This analysis included the 17 patients from the OxQUIP study (labelled "OxQUIP 2018" in the figure) who were not on other antiparkinsonian medications. These 17 patients showed a mean prolongation of 15.6 ms when on relative to off levodopa (95% confidence interval 1.8–29.4 ms). The meta-analysis yielded a very similar mean prolongation of 15.8 ms (95% CI 3.7–27.9 ms).

We then repeated the analysis, this time adding in 3 remaining studies which included patients who were taking other anti-parkinsonian medications in addition to levodopa. All 38 PD patients in the OxQUIP cohort described here were included in this analysis. In these 38, there was a mean prolongation of PSL that was similar to that for levodopa only patients at 13.3 ms (95% CI 3.0–23.7 ms). In the meta-analysis, the mean prolongation was slightly longer, at 16.7 ms (95% CI 4.8–28.6 ms).

Fig. 1G shows the changes in PSL for each PD participant in the OxQUIP study, ordered by the magnitude of the change. The levodopa-only cases are shown with open bars while the multiple medications cases are shown by filled bars. There was no significant difference in the magnitude of the change between these two groups ($p = 0.23$, Mann Whitney *U* test).

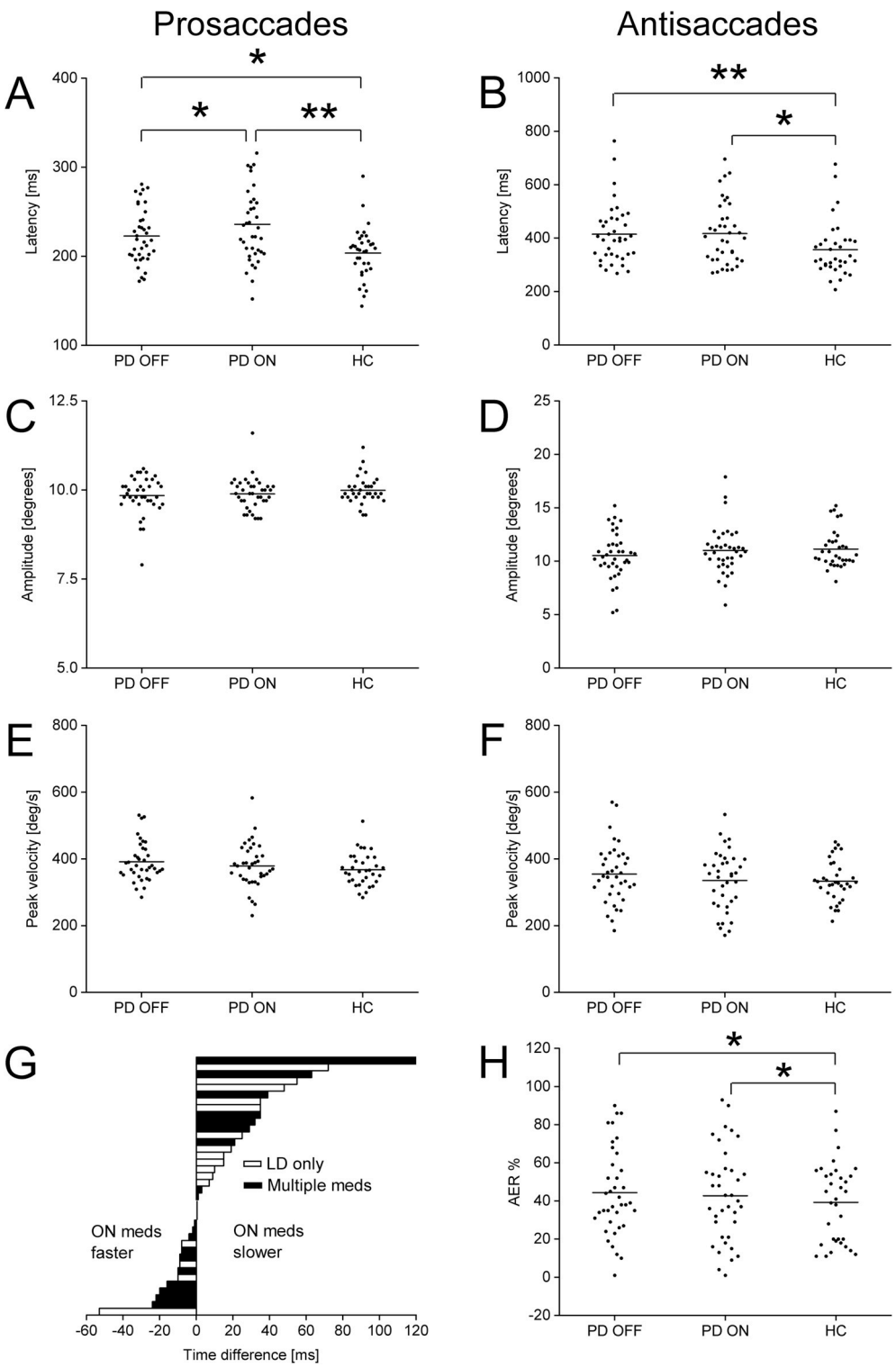

Fig. 1. Saccadic parameters for all participants. Abbreviations: PD OFF, Parkinson's patient while off medication; PD ON, Parkinson's patient after medication administered; HC, Healthy control; LD, levodopa. * denotes $p < 0.05$ and ** denotes $p < 0.01$. Panel G: diverging bar chart showing changes in PSL. Bars extending to the right signify increased PSL with medication. Open bars represent patients challenged with levodopa only, while filled bars represent those with multiple medications.

3.3. Correlation of antisaccadic latency with UPDRS

Given that ASL appears unaffected by medication, but strongly affected by the presence of disease, it may be a good candidate as a disease severity marker. We therefore examined whether ASL is correlated with the motor component of the MDS-UPDRS. Fig. 3 shows this relationship for PD patients both off and on medication. In both cases there is a significant positive correlation between MDS-UPDRS part III and ASL (PD OFF: r = 0.42, $p = 0.0094$; PD ON: r = 0.49, $p = 0.0017$).

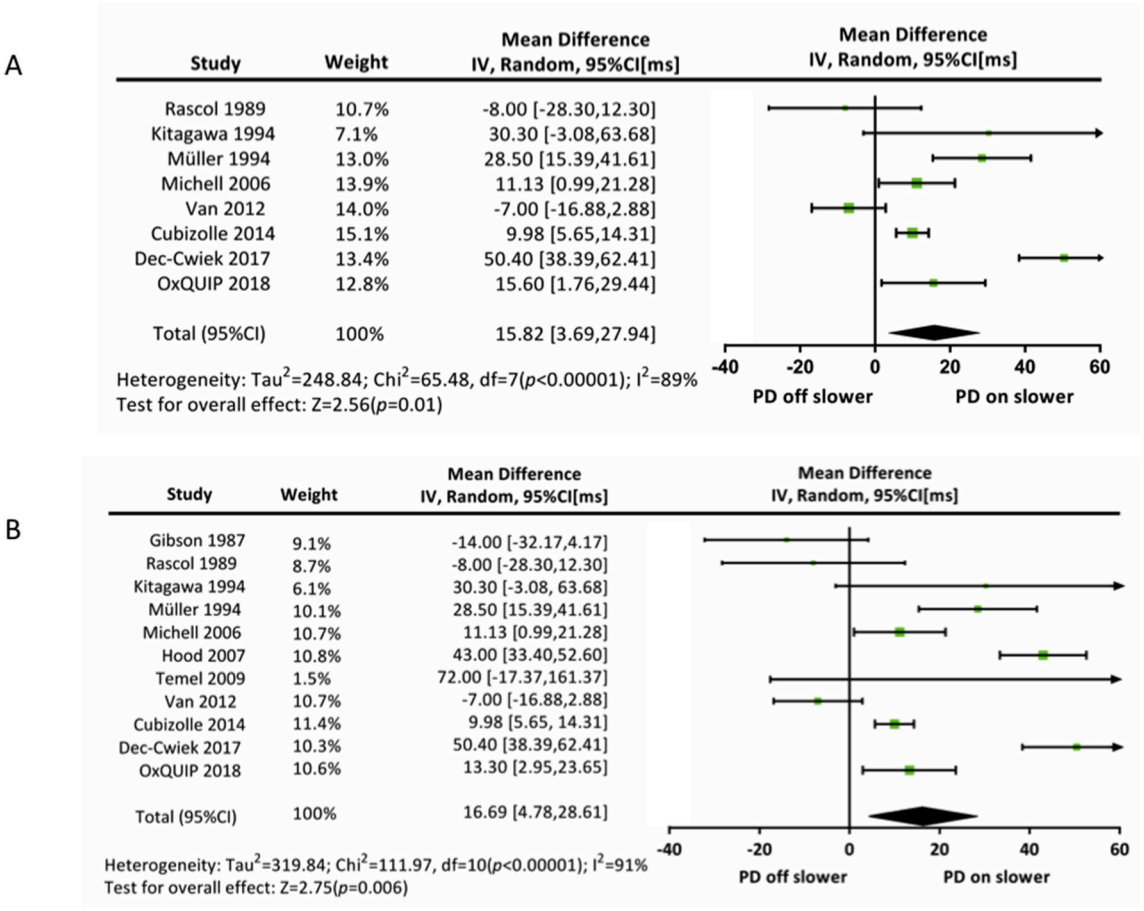

Fig. 2. Meta-analysis of the effects of antiparkinsonian medication on prosaccadic latency. **A:** effects of levodopa treatment only. **B:** effects of combined antiparkinsonian medication. In both cases there is a prolongation of latency, to a slightly greater degree with multiple medications than with levodopa alone.

4. Discussion

Accurate and objective biomarkers are essential in trials of new therapeutics. In studies where a novel/test drug is added to the standard of care, an accurate understanding of how the marker is affected by background symptomatic medication is critical. When evaluating new symptomatic treatments, markers sensitive to the effects of medication are clearly desirable.

PSL is the most widely examined saccadic parameter in PD, and the central finding from this study is that levodopa, with or without other antiparkinsonian medications, increased PSL. There was no significant difference in the magnitude of the increase between levodopa-only participants and those who were taking multiple dopaminergic medications. In the whole PD cohort in this study PSL was increased by

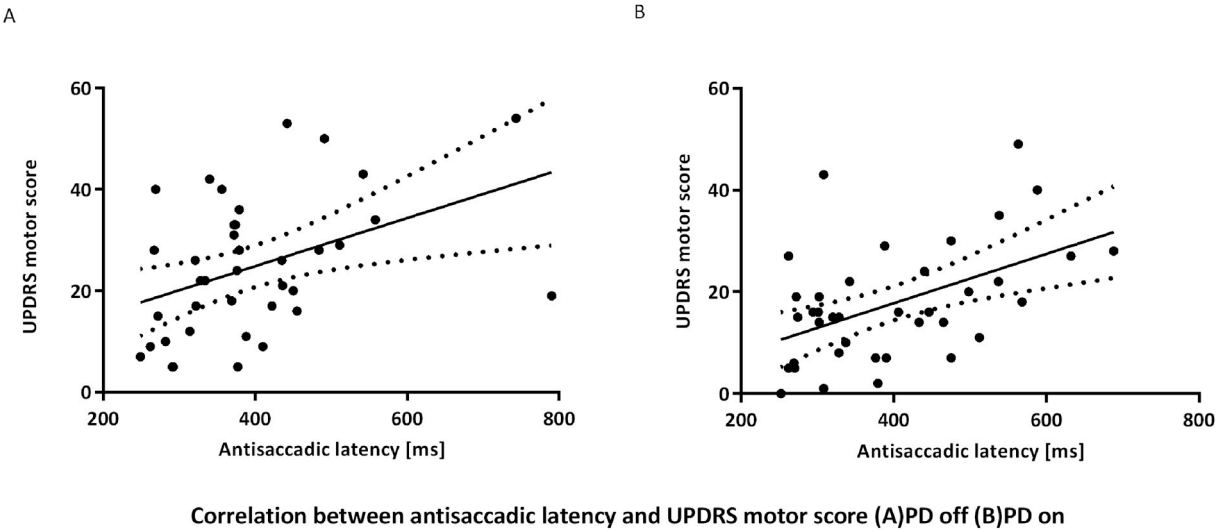

Fig. 3. Scatterplot showing the interaction between ON/OFF UPDRS and the antisaccadic latency (ASL). A: Off medications and B: On medication. The solid lines are linear fits and the dotted lines indicate the associated 95% confidence bands.

medication by slightly over 5% ($p = 0.010$). Medication produced no statistically significant change in other saccadic parameters. There was a non-significant trend to lower velocities (both PPSV and PASV) in the medication-on state. There was no change in saccadic amplitude, which is perhaps surprising given that this has been previously shown to be affected by medication both in humans [29,30] and in monkeys [31,32]. A possible explanation for this discrepancy may be the nature of the task we have chosen: demonstrating an effect on amplitude may require a memory-guided saccadic task or a task involving multiple targets primarily in the horizontal plane.

We have meta-analysed the results of published studies to date to yield a best estimate of the effects of medication on PSL from all the available data. In this analysis we have distinguished between studies reporting the effects of levodopa alone, and those reporting the effects of multiple antiparkinsonian medications. The results of the meta-analysis match those of this study in terms of direction of change, although there are some modest differences in degree. The difference in PSL prolongation in the two meta-analyses was small (less than 1 ms) and non-significant.

The motor and oculomotor pathways bear many similarities and analogous components. Both feature cortico-basal ganglia loops incorporating areas of frontal neocortex that project to the striatum, with onward projections from there to the pallidum, and eventual return to the cortex via the thalamus. Both pathways are affected by PD, and PD results in hypokinesia in both somatic and ocular motor tasks. It is remarkable therefore that levodopa affects the two in a qualitatively different way. However it is not the only paradoxical physiological effect of PD treatment on eye movements; it has been shown that deep brain stimulation and lesions at the same site both improve motor symptoms of PD yet have precisely opposite effects on saccadic latency [33]. Further work is needed in order to better understand the physiological basis for these effects. In particular, measurements of internally generated prosaccades, such as in a memory guided saccadic (MGS) task, would be interesting. Memory guided saccades are known to be initiated by the direct pathway in the basal ganglia [34]. There is some evidence of shortening of latency [35] when using such a paradigm, in contrast to the lengthening of latency for externally cued saccades seen here.

In contrast to symptomatic treatments, for candidate disease modifying drugs (DMDs), markers should be resistant to medication effects if possible. Investigators in DMD trials are likely to be looking for small changes in disease trajectory over time, which can easily be concealed if the background treatment substantially affects the marker. The use of the Unified Parkinson's Disease Rating Scale (UPDRS) score in trials evaluating candidate DMDs illustrates the problem [36]. In trials in unmedicated PD patients [37,38] one can see a clear progression in the UPDRS over time, confirming the ability of the UPDRS to track disease progression and therefore to potentially detect changes in trajectory. However, the presence of dopaminergic medication completely obscures this progression [39]. If a biomarker is unable to demonstrate disease progression then neither will it be able to detect changes in the rate of that progression due to the candidate DMD. Even if symptomatic medication does not completely obscure the disease progression signal, variations in medication levels may be a potent source of noise in trial data, particularly in a disease such as PD in which gut motility is affected and medication levels can change unpredictably.

There are two potential solutions to this problem. The first would be to perform all assessments in DMD trials off background symptomatic medication. While possible, this is onerous for participants, and while levodopa will wash out in a few hours, considerably longer may be needed to ensure complete elimination of some dopamine agonists. This approach may therefore be poorly tolerated, and secondary effects such as fatigue and anxiety, resulting from the cessation of normal medication, may themselves have a confounding effect on measurements.

The second approach is to look for a marker that is less affected, or ideally completely unaffected, by background symptomatic treatment, yet still reflects the presence and progression of the underlying disease.

In this study, we found that medication left the antisaccadic parameters ASL and AER almost unchanged (medication increased ASL by 0.55% and produced a 1.1% increase in AER; neither change was statistically significant). This contrasts with a previous study that suggested an improvement in AER with medication [22]; further studies are needed to clarify this [22]. Interestingly, an earlier study has shown that administration of levodopa to healthy controls [41] results in an increase in antisaccadic errors but no change in pro- or antisaccadic latencies.

While ASL appears hardly to be affected by symptomatic medication at all, it is very clearly affected by the disease. The nonsignificant change of 0.55% due to dopaminergic therapy contrasts sharply with a 16% difference between patients off medication and controls. This mirrors the earlier results of Hood et al. [22] who found a 1.4% medication effect but 36% disease effect on ASL. This is therefore an ideal combination of characteristics for a DMD trial biomarker. It potentially obviates the need to withdraw symptomatic treatment, and eliminates one major potential source of noise from the trial data.

That does not of course necessarily imply that a quantity like ASL alone can provide sufficient signal to noise to function as a sole marker in a DMD trial. There may be several sources of noise in the data other than medication, for example time of day or patient fatigue. The effect of these may be large enough to obscure the signal unless the sample size used is very large. However, a marker that is sensitive to the presence of disease but resistant to medication effect is at the very least a good starting point, and even if not sufficient for the task by itself, it is likely to be useful in combination with other carefully chosen variables.

It is striking that PSL is affected by medication yet ASL is not. The simplest potential explanation for this would be that dopamine is affecting the retinocollicular pathway, as this is the only part of the prosaccadic circuit that is not also involved in antisaccades. The effect of dopamine on the superior colliculus has been the subject of recent research [42]. Bolton and colleagues have described a dopaminergic modulatory pathway terminating in the SC. It has been previously shown that the SC contains higher concentrations of dopamine than for instance in the frontal cortex and the hippocampus [43]. These findings open new avenues of investigation into how the arrangement in the SC of both dopamine axons and receptors affect behaviour [42], and add to the complexity of the effects of dopamine on brain function.

4.1. Limitations

Our study had a number of limitations. First, overall the patients were early in the disease course (mean duration 2.9 years) and validation in longer duration groups is needed. Second, this was not a longitudinal study, and therefore cannot provide evidence regarding the ability of saccadic parameters to track disease progression. The correlation between ASL and MDS-UPDRS motor score suggests that as disease progresses, so should ASL, but this will require verification in a longitudinal study. Third, some participants had very high AER, in a few cases over 90%, meaning that the number of trials available from which to calculate the parameters of (correctly executed) antisaccades was low. Fourth, while conducting the meta-analysis we found substantial heterogeneity in the literature, present both in the saccadic paradigms used and also the data provided in the existing literature, which limited our ability to meta-analyse a large number of studies.

5. Conclusions

Saccadic parameters have been widely proposed as biomarkers in PD. Their usefulness (for example in clinical trials) depends on having an understanding of how they are influenced by background medication. The effect of medication on PSL has been controversial; both this study and a meta-analysis of this and previous studies show that dopaminergic medication prolongs prosaccadic latency significantly. By

contrast, such medication does not affect antisaccadic latency, raising the prospect that this might be a very useful tool. Further studies, especially longitudinal ones, are needed.

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Declaration of competing interest

The authors declare no conflict of interest.

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Appendix 1. Authors' contributions.

Name	Location	Role	Contribution
Zhongjiao Lu	University of Oxford	Author	Acquired some of the data and analysed the data; helped with some of the drafting of the manuscript for intellectual content
Tim Buchanan	UCB Biopharma SPRL, Brussels, Belgium.	Author	Revised the manuscript for intellectual content and statistical analysis
Chris Kennard	University of Oxford	Author	Revised the manuscript for intellectual content
James FitzGerald	University of Oxford	Author	Design and conceptualized study; analysed some of the data; performed statistical analysis, drafted the manuscript for intellectual content
Chrystalina Antoniades	University of Oxford	Author and leading the study	Design and conceptualized study; acquired some data, analysed some of the data; performed statistical analysis, drafted the manuscript for intellectual content and is responsible for the final draft

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