

## Research Report

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# The Relationship between Abnormalities of Saccadic and Manual Response Times in Parkinson's Disease

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### Abstract.

**Background:** Clinicians normally use subjective rating scales to estimate the impairment of patients with Parkinson's disease (PD). More objective and quantitative methods of assessment would greatly aid our understanding of the disease. One promising approach is to measure reaction time: the large amount of data recorded in a short period provides precise, reproducible evaluation of the underlying neural decision processes. Manual evoked reaction times and repetitive tapping speed are often used, but differences of experimental design and analysis tend to obscure their interpretation. Saccadic latency, in many ways a simpler and more standardised task, is also normally affected in PD, but its relation to the kind of movement impairment that affects patients' quality of life is less obvious.

**Objective:** The aim of this study was to evaluate these tasks in detail and also see whether their use in combination could provide a better measure than each in isolation.

**Methods:** We compared three reaction time tasks: saccadometry, and evoked and spontaneous tapping, using protocols as similar as possible, correlating the measurements within a group of PD patients and of age-matched controls.

**Results:** Surprisingly, manual and saccadic performance is uncorrelated in the normal population; but both are similarly affected by PD. The differences between groups are strengthened when the three measures are combined.

**Conclusions:** Saccadic latency can be regarded as an appropriate surrogate for more general kinds of motor impairment. The combination of saccadic and manual parameters enhances their potential use in quantifying disease status and evaluating treatments.

Keywords: Saccadic eye movements, manual reaction times, Parkinson's disease, evoked motor response

## INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder that has as part of its core pathology the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) [1]. Whilst it is now recognised to have non-nigral pathology and a

range of non-motor features, nevertheless the classical presentation is primarily as a movement disorder: bradykinesia, rigidity and tremor, and abnormalities of eye movements, especially saccades. The mechanisms underlying these motor disorders remain poorly understood.

Two major problems currently hinder research in this area. First, the increasing number of Parkinsonian-like conditions that must be distinguished, and the likelihood of PD sub-types – no doubt at least in part genetically determined – that demand personalised treatment and forbid over-generalised theories

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of causation. Second, the need to distinguish the effects of the disease from the effects of the medication used to treat it, especially as this too may be idiosyncratic to individual patients. Conventional, subjective measures of impairment, when performed by an experienced clinician, are of course central to assessing disease, and will remain so. But it would be desirable to supplement them by standardised tests of motor performance capable of generating genuinely quantitative data, but which can be performed quickly and easily in the clinic rather than in specially-equipped laboratories. A kind of test that seems especially promising in this respect is the measurement of reaction time: either of simple manual responses, evoked by visual stimuli, or spontaneously generated, as in measures of tapping speed, or of saccades. The advantage of the latter is that saccades are exceptionally stereotyped movements that can be performed in rapid repetition without significant fatigue (since in everyday life we make two or three saccades every second). The control of saccades is also intimately bound up with the neural structures most affected by PD. Frontal and parietal cortical areas project directly to the superior colliculus and frontal areas project indirectly through a basal ganglia pathway that includes the caudate nucleus and substantia nigra pars reticulata (SNpr). The substantia nigra and related brainstem areas have been suggested to play a crucial role in various types of saccadic eye movements by mediating a dopamine-related descending input from the frontal cortical areas to the superior colliculus [2].

Many previous studies have demonstrated that performance in both evoked or spontaneous tasks is systematically impaired in PD. In evoked manual tasks, both mean latency and intra-individual variability in untreated patients with PD appears to be increased relative to controls [3, 4] from the earliest stages of the disease. Other studies have examined spontaneous finger tapping [3, 5–8] and qualitative hand-tapping and in both abnormalities have been noted in idiopathic PD (IPD) patients [9–11]. Similarly, saccadic latency can be increased compared to controls both in simple tasks [12–15] and more complex tasks such as anti-saccades [16–21], and can sometimes provide quantitative differences that may differentiate PD from other neurodegenerative conditions. Mossman and colleagues showed that impairments in simple saccadic tasks may be helpful for differential diagnosis, being minimal when either cortical (Alzheimer's disease) or nigrostriatal neurodegeneration (PD) exists on its own [22], but more prominent when combined in a single pathological disease process, as occurs in PD

with dementia (PDD). Saccadic tasks could be used to increase the accuracy of the differential diagnosis of Parkinsonian syndromes including PSP [23], and a small pilot study on PD and Parkinsonian plus syndromes patients found that saccadic latencies were longer for PSP than for PD patients [24].

Of the two kinds of task, manual responses are of course more directly related to the kinds of general motor impairment that affect the patient's quality of life, and therefore perhaps likely to be more attractive to the clinician. But from a scientific point, the lack of standardisation of test protocols and conditions means that it is difficult to compare results from different laboratories, or create from them universal measures of impairment, comparable to the UPDRS. Saccades, on the other hand are increasingly being performed with highly standardised protocols, and in general we have a better knowledge of the underlying neural mechanisms that generate them.

It seemed to us therefore that it was desirable to make a direct comparison between reaction times for saccades, and for the two major classes of manual response (evoked and spontaneous), using protocols and analytical methods as near identical as possible, in order to obtain quantitative information about how these different measures relate to one another, and how they are affected by the disease itself.

## MATERIALS AND METHODS

### *Participants*

This study, conducted at the Centre for Brain Repair, Cambridge, UK, was approved by the Cambridge Regional Ethics Committee. Participants were recruited from the regional Parkinson's disease research clinic at the Centre. All participants gave their written informed consent after the procedures were explained to them.

Two groups were examined: (a) Parkinson's disease (PD) patients; and (b) a control (C) group. The PD group consisted of 97 individuals with mean age of 65.18 years, the control group of 39 individuals with an average age of 62.54 years (Table 1). The control group comprised the spouses of the patients who had no known neurological condition at the time of testing. None of the controls were taking any medication at the time of testing; the patients were receiving their usual medication for their PD. All participants undertook manual alternation and saccadic tests; and a subset of 21 PD and 15C (Table 2) additionally performed an evoked manual reaction-time task.

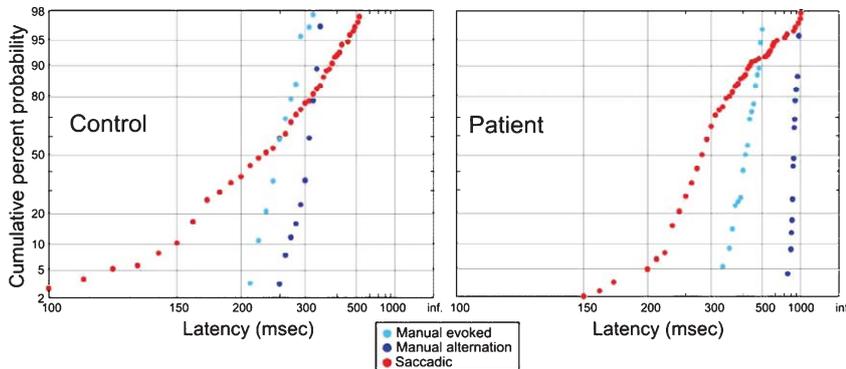


Fig. 1. Reciprobit plots. Reaction time distributions are plotted as cumulative histograms on a probit scale, as a function of reciprocal latency; when the rate of the underlying process, and thus reciprocal latency, are normally distributed, the data will lie on a straight line is generated. Here, data for a typical control (left) and a typical patient (right) are shown, performing each of the three tasks: saccades, evoked manual responses, and manual alternation. For the patient, a small sub-population of early responses can be seen in the case of the saccadic tasks, visible as a reduction in slope for the shortest latencies.

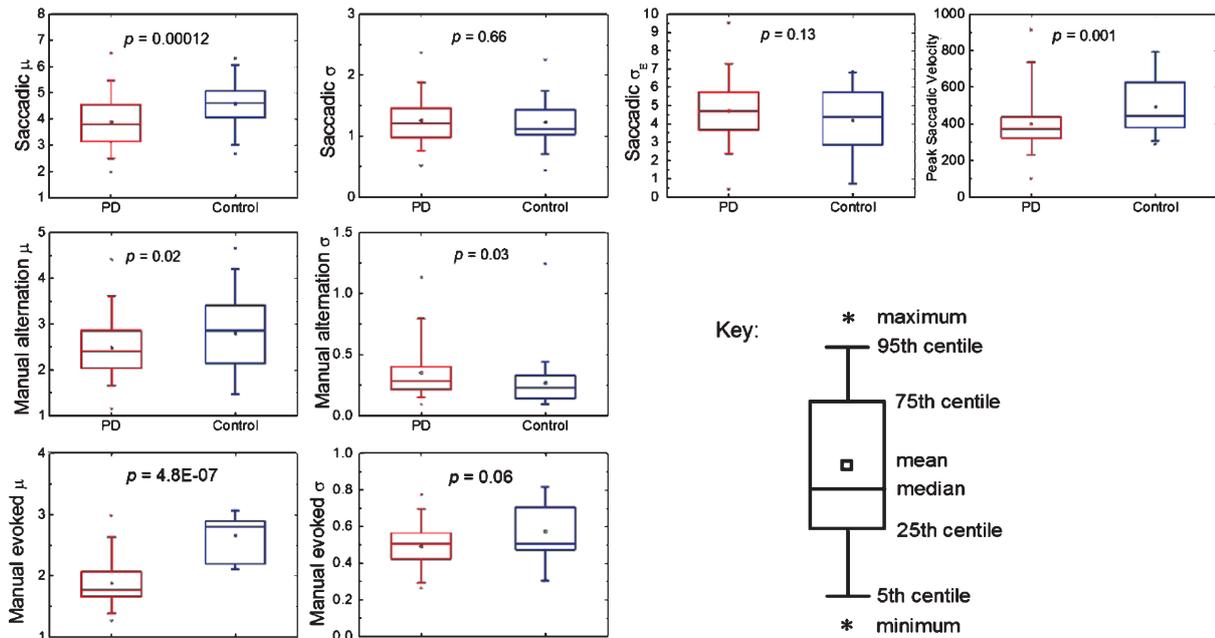


Fig. 2. Box plots of measured parameters in the saccadic, manual alternation and manual evoked tasks ( $\mu$ ,  $\sigma$ ; for saccades only,  $\sigma_E$ , peak saccadic velocity) for PD patients (red) and controls (blue). (Units are  $s^{-1}$  apart from peak saccadic velocity, which is in  $deg s^{-1}$ ). In each case the  $p$  value for a comparison of means (unpaired  $t$ -test) is shown.

Recording techniques

Horizontal saccadic eye movements were recorded in a standardised 10 degree step task using a miniaturised infra-red 1 kHz saccadometer (Ober Consulting, Poznan, Poland; [25]). The recording methods have been previously described [26]. The evoked manual reaction-time measurements were made with the same saccadometer device but switching to its man-

ual mode, in which the stimuli consist of yellow LEDs mounted on the left and right of the control box, with corresponding push buttons below them. The control box was held by the participant (the distance between the LEDs then being some 5 deg), who was instructed to respond to the appearance of the left or right LED by pressing the appropriate left or right button (using the left and right thumbs) as quickly as possible. For both saccadic and manual

Table 1

Saccadic and manual alternation task, showing the measured parameters  $\mu$ ,  $\sigma$ ,  $\sigma_E$ , peak saccadic velocity) for the PD and control groups, together with clinical evaluations. (Means  $\pm$  1 SE; N/A: not applicable)

	PD ( $n=21$ )	C ( $n=15$ )
Age: mean $\pm$ SD	69.62 $\pm$ 6.40	67.67 $\pm$ 11.71
M:F ratio	8:13	6:9
<i>Saccades</i>		
$\mu$ ( $s^{-1}$ )	4.03 $\pm$ 0.23	4.75 $\pm$ 0.19
$\sigma$ ( $s^{-1}$ )	1.21 $\pm$ 0.06	1.19 $\pm$ 0.06
$\sigma_E$ ( $s^{-1}$ )	4.14 $\pm$ 0.43	3.65 $\pm$ 0.43
<i>Manual alternation</i>		
$\mu$ ( $s^{-1}$ )	2.42 $\pm$ 0.12	2.82 $\pm$ 0.14
$\sigma$ ( $s^{-1}$ )	0.33 $\pm$ 0.03	0.29 $\pm$ 0.06
<i>Manual evoked responses</i>		
$\mu$ ( $s^{-1}$ )	1.90 $\pm$ 0.10	2.67 $\pm$ 0.08
$\sigma$ ( $s^{-1}$ )	0.50 $\pm$ 0.03	0.58 $\pm$ 0.04

Table 2

The measured parameters, as in Table 1, for sub-groups of patients and controls who undertook the manual evoked response task. (Means  $\pm$  1 SE).

	PD ( $n=97$ )	C ( $n=39$ )
Age: mean $\pm$ SD	65.18 $\pm$ 8.12	62.54 $\pm$ 12.12
M:F ratio	52:45	18:21
<i>Saccades</i>		
$\mu$ ( $s^{-1}$ )	3.93 $\pm$ 0.09	4.63 $\pm$ 0.13
$\sigma$ ( $s^{-1}$ )	1.27 $\pm$ 0.04	1.24 $\pm$ 0.05
$\sigma_E$ ( $s^{-1}$ )	4.76 $\pm$ 0.17	4.22 $\pm$ 0.32
Peak saccadic velocity (deg $s^{-1}$ )	404 $\pm$ 15	499 $\pm$ 25
<i>Manual alternation</i>		
$\mu$ ( $s^{-1}$ )	2.51 $\pm$ 0.06	2.83 $\pm$ 0.14
$\sigma$ ( $s^{-1}$ )	0.36 $\pm$ 0.02	0.28 $\pm$ 0.03
<i>Clinical</i>		
Hoehn and Yahr	1.80 $\pm$ 0.07	N/A
UPDRS (motor score) $\pm$ SE	15 $\pm$ 1.01	N/A
MMSE	28.53 $\pm$ 0.22	N/A

measurements, 300 trials were recorded over a period of 10–15 minutes.

To measure spontaneous manual alternation times, participants sat in front of the hand-tapping device, a box with two push-buttons projecting from the top 30 cm apart, one red and one green [27]. They were instructed to tap the buttons alternately as fast as possible over a 45-second period; software on a laptop connected to the device recorded the latency between each tap and the preceding tap. Both hands were tested separately, the dominant hand being tested first. The successive intervals between taps were recorded for each hand separately, to generate histograms of the distribution of intervals between consecutive taps.

Saccadic and hand tapping assessments were undertaken at the same time as the clinical assessments (Unified Parkinson's Disease rating scale – UPDRS

motor part, Hoehn and Yahr and Mini-Mental state examination – MMSE) so as to collect all the data in a single test session for each participant.

### Data analysis

The basic method for analysing reaction time distributions has been previously described [26]. They are based on estimation of the parameters of the supposed underlying LATER model ([www.cudos.ac.uk/later.html](http://www.cudos.ac.uk/later.html)) parameters, in which a decision signal rises in response to a stimulus at a rate  $r$  until it reaches a threshold, initiating a response:  $r$  varies randomly from trial to trial, with a Gaussian distribution of mean  $\mu$  and variance  $\sigma$  [28]. Sometimes an additional sub-population of early responses can be seen, which can be modelled by a LATER unit of variance  $\sigma_E$  and mean zero. These three parameters are estimated by minimisation of the Kolmogorov-Smirnov one-sample statistic; it is worth noting that  $\mu$  is also the best-fit estimate of the reciprocal of the median latency. The same procedure was followed for the latencies of evoked saccades, evoked manual responses, and the inter-tap intervals in spontaneous manual alternation; since no early responses were seen in either manual task, the parameter  $\sigma_E$  was not used.

## RESULTS

Figure 1 shows data for a typical control and a typical PD patient, performing each of the three tasks: saccades, evoked manual responses, and manual alternation. For the PD patient (Fig. 1 right), a small sub-population of early responses can be seen in the case of the saccadic tasks, visible as a reduction in slope for the shortest latencies.

Figure 2 compares the results in the three tasks (evoked saccades, evoked manual responses, manual alternation) for PD patients and controls: the parameters (whose distributions did not differ significantly from normal: Shapiro-Wilks test,  $p < 0.05$ ) were compared for the two groups using unpaired  $t$ -tests, the results of which are shown on each graph. Tables 1 and 2 show the means and standard errors (SE) of the parameters plotted in the graphs. For each of the three tasks the value of  $\mu$  is smaller for the patients, meaning that their responses are significantly slowed: the effect is particularly marked for evoked manual  $\mu$  ( $p < 10^{-6}$ ): in terms of specificity/sensitivity analysis this corresponds to a 28% false positive rate with 90% of patients correctly identified. By taking this parameter together with the other most significant discriminator, saccadic

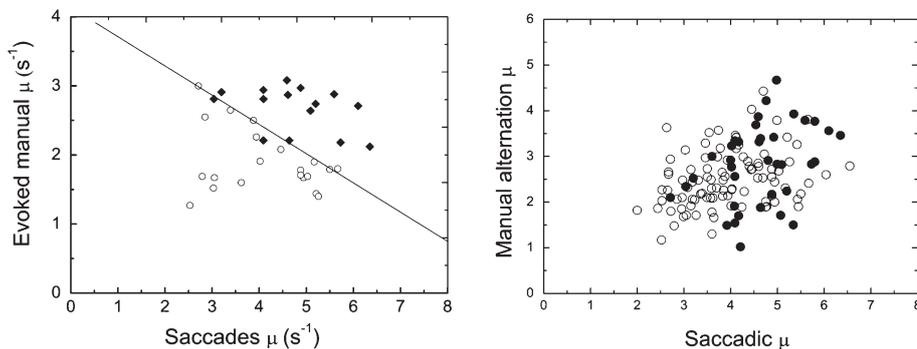


Fig. 3. *Left*: Evoked manual  $\mu$  plotted against saccadic  $\mu$ . PD patients (open circle) form a distinct cluster from controls (black diamond). The best-fit line of discrimination for the two groups is shown. *Right*: Correlation of parameter  $\mu$  (reciprocal median latency) for manual alternation and saccades in the PD group (open circle) and controls (black diamond). For the PD group the correlation is statistically significant ( $R=0.31$ ,  $p=0.02$ ), but not for the controls, suggesting that it is due to both latencies being increased in the patients.

$\mu$ , the patients and controls can be divided even more clearly into two distinct clusters (Fig. 3 *left*) with only a 14% false positive rate at a detection rate of 95%. For the parameter  $\sigma$  the only significant difference observed was for manual alternation.

Figure 3 *right* shows the relation between the values of the parameter  $\mu$  for the saccadic and manual alternation tasks, in PD patients: the correlation is statistically significant ( $R=0.31$ ,  $p=0.02$ ). Also, the relation between the alternation manual responses  $\mu$  and manual evoked  $\mu$  is statistically significant ( $R=0.54$ ,  $p=0.01$ ) while the difference between saccadic  $\mu$  and manual evoked responses  $\mu$  is not significant ( $R=0.21$ ,  $p=0.35$ ).

The UPDRS motor score, Hoehn and Yahr staging, Mini-mental state examination (MMSE) and levodopa-equivalent units were plotted against the three ( $\mu$ ,  $\sigma$  and  $\sigma_E$ ) saccadic parameters, the two ( $\mu$  and  $\sigma$ ) spontaneous hand-tapping parameters and the two ( $\mu$  and  $\sigma$ ) evoked manual parameters. No significant correlation was found in any case.

## DISCUSSION

In this study we have examined a group of medicated PD patients and normal age and sex matched controls performing three different reaction time tasks: saccadic, evoked manual and spontaneous manual alternation. For each task, the PD patients were significantly slower than age-matched controls, as shown by reduced values of the LATER parameter  $\mu$  the mean rate of rise of the underlying decision signal. Combining data from the saccadic and evoked manual tasks provided particularly good discrimination between patients and controls. A striking finding con-

cerns the relation between saccadic and evoked manual latency. Although these are significantly correlated within the patient group, this is not the case for the controls (Fig. 3). The conclusion, perhaps unexpectedly, is therefore that in the normal population these two kinds of reaction times vary independently, but that – on the contrary – the effect of PD is the same for both (a reduction of  $\mu$ ) implying that saccadic latency appears to be affected in a similar way to manual reaction time, justifying its use as a surrogate for the measurement of general motor impairment.

In summary, the speed of performance in a range of saccadic and tapping tasks is significantly affected in PD, and discrimination between patients and controls is enhanced by using combinations of results from more than one kind of task. Different kinds of reaction time appear not to be correlated in the normal population, yet they are affected in a very similar way as a result of the disease. This greatly increases confidence in using saccadic latency as a general measure of motor impairment in PD. The speed and objectivity of saccadic latency measurements has the quantitative characteristics needed to help to distinguish between sub-classes of pathology; in particular, this approach has the potential to provide quantitative measures for monitoring individual responses to particular therapies, and to undertake the urgently-needed investigation of the changes with medication from a drug-naïve state, that currently confound research in this area.

### *The effects of medication in Parkinson's disease patients and healthy controls*

One of the major problems in the interpretation of eye movement studies in neurodegenerative disease

is how to disentangle the effects of the disease itself from those of the medications used to treat it. Studies on patients with PD have given mixed and at times conflicting accounts of the effects of dopaminergic medication on saccadic eye movements. Michell et al. [15], and Hood et al. [29] found that levodopa prolonged prosaccadic latencies, although the effect varied among the subjects. By contrast Nakamura et al. found no significant effect of dopaminergic medication on prosaccades [30]. Other reported effects of levodopa include a reduction in the error rate for antisaccades [29], and improvement of prosaccadic accuracies [31] and amplitudes [32].

One might wonder what happens after administration of such medication to healthy controls. A study by Duka and colleagues [33] examined twenty young healthy male volunteers, using antisaccades and reflexive saccade tasks. All the participants received levodopa and benserazide (100 and 25 mg respectively) and antisaccades and reflexive saccades were measured after 1 and 5 hours. There was an increase in antisaccadic errors but no change in pro- or antisaccadic latencies.

It is evident that great care is needed when analysing eye movement paradigms in relation to neurodegenerative disorders, particularly when interpreting differences between groups of treated patients and healthy individuals. All too often it is assumed that differences between these groups are primarily related to disease progression when in fact most medications used to treat neurological and psychiatric disorders have established effects on eye movement disturbances. The effects of pharmacological treatments on eye movement control not just in PD, but also in a range of other conditions including schizophrenia and affective disorders, have been reviewed by Reilly and colleagues [34].

In addition, a number of studies have looked at quantifying motor deficits in PD by using repetitive sequential tasks such as finger tapping [3–5, 7, 8] and hand tapping [9, 35, 36]. A study by Camicioli et al. [4] suggests that there is increased intraindividual inter-tap interval variability in a group of untreated PD patients, at the earliest stages of the disease. This is a very interesting study, as it is one of the few that report results on patients naive from medication and at the earliest stages of the disease. Ongoing follow up of these patients following the initiation of treatment is of great importance as it will shed light upon how the test is affected by dopaminergic medication.

Both saccadic and tapping tasks, could be of immense use if one is able to extract the effects that

coexist in any cohort of patients who are taking different types of medication. On one hand, eye movement drug effect seems to have been the focus of a number of studies providing invaluable information for ongoing studies. On the other hand, tapping (manual or evoked), although frequently used as an assessment of motor dysfunction in PD and very easy to administer, has been less investigated in relation to the dopaminergic medication effects. The very few studies that have addressed medication effects by using untreated PD patients have not reported on longitudinal studies in these cohorts. Larger longitudinal studies are essential, and in particular studies that begin with untreated patients at the earliest stages of the disease so to allow the follow up of both disease progression but also that of administration of medication.

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## CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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