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Response times for visually-guided saccades in persons with Parkinson's disease: A meta-analytic review

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Short title: Visually-guided saccades in Parkinson's

Summary

Individuals with Parkinson's disease (PD) show marked impairments in their ability to generate self-initiated, or "voluntary", saccadic eye movements. Investigations of visually-guided, or "reflexive", saccades have, on the other hand, produced inconclusive results with studies showing response times (RTs) in persons with PD that are slower, faster, or indistinguishable from those of controls. We performed a meta-analysis to establish whether there are consistent effects of PD on the metrics of visually-guided saccades. Combining results across 47 studies we found that reflexive saccades are overall initiated more slowly in persons with PD than in controls, however, this analysis also revealed considerable heterogeneity across studies. Step-

wise meta-regression, using eleven potential predictors, subsequently showed that differences in mean RT between controls and persons with PD may arise due to aspects of experimental design. In particular, mean target eccentricity was shown to impact substantially on RTs such that persons with PD predictably initiate saccades faster than controls at small target eccentricities, while responding more slowly for large target eccentricities. Changes in eye-tracking and display equipment over the period covered by the review were also found to have impacted on the pattern of results obtained. We conclude that a, previously unsuspected, eccentricity effect could explain why the saccadic eye movements of persons with PD are sometimes found to be "hyper-reflexive" compared to controls, and suggest that this effect may arise due to PD-induced changes in both peripheral perceptual processing and in central executive mechanisms involving the basal ganglia.

Key-words: Parkinson's disease, saccadic eye movements, oculomotor function, basal ganglia, meta-analysis

Introduction

The study of eye movements provides one of the most important investigative windows for understanding the function, and dysfunction, of the human brain (van Gompel, 2007). Within this research paradigm a particular focus of interest has been on saccade control in Parkinson's disease (PD). For instance, clear differences have been identified in the metrics of *self-initiated*, or "voluntary", saccades generated by individuals with PD as compared with age-matched controls (Kennard and Lueck, 1989), and, together with related findings on oculomotor control in PD, this evidence has helped inform theoretical accounts of PD pathophysiology (McAuley, 2003). On the other hand, despite considerable research effort, studies of response times (RT) for *visually-guided*, or "reflexive", saccades, with unpredictable target location and/or onset time, have produced inconsistent findings—there have been reports of longer (Shimizu et al., 1981; Warabi et al., 1986; White et al., 1983), shorter (Bekkering et al., 2001; Briand et al., 2001; Kingstone et al., 2002), and statistically indistinguishable (Kimmig et al., 2002; Lueck et al., 1992; Rottach et al., 1996) RTs in persons with PD compared to their peers. The current article seeks to address this controversy through meta-analysis. Our aim is not only to better quantify the effect of PD on visually-guided saccadic RT, but also to find an explanation for the heterogeneity of past findings on this topic. We will contend that the results of this analysis have important implications both for our understanding of PD and for the use of eye movement studies in neuropsychological research.

Many of the symptoms of PD are due to the loss of dopamine input to the basal ganglia (BG) (see Zigmond, 2002, for review; though also see Braak et al., 2003) for

other possibilities). Anatomical and functional studies show that the BG interact with both cortical and sub-cortical oculomotor structures and perform an important role in gating saccadic commands (Hikosaka et al., 2000; McHaffie et al., 2005). Several authors have suggested that the effect of PD upon the latency of visually-guided saccades is non-existent, or at least small, compared to typical levels of variation in human adults and to the marked effects seen in self-initiated saccades (Kennard and Lueck, 1989; Tanyeri et al., 1989). From a neuroanatomical perspective, however, there is no compelling reason to expect that the two saccade types are differentially gated by the BG, therefore, in the absence of the relevant empirical data, one might have expected that both classes would be similarly affected by neurodegeneration in PD. How, then, can we understand the lack of evidence for a clear effect in studies of visually-guided saccades conducted thus far? Past investigations have often focused on one easily-manipulated experimental variable—the time that is allowed to elapse between the offset of the fixation stimulus and the onset of the target stimulus. Specifically, three particular experimental paradigms involving this variable have been widely studied: the *gap* paradigm, in which the fixation stimulus is extinguished some time before the presentation of the target stimulus; the *step* paradigm, in which fixation offset and target onset are simultaneous; and the *overlap* paradigm, in which the fixation stimulus is presented continuously or extinguished some time after target onset (Figure 1). These paradigms are known to give rise to significant differences in saccadic RT (Kalesnykas and Hallett, 1987; Saslow, 1967), and thus the effects of stimulus timing are commonly studied.

However, research on oculomotor control in PD has been conducted for over three decades, and during this time experimental designs have also differed in many other

respects. In particular, changes in technology for eye-tracking and stimulus display have had a major impact on how experiments are conducted. For instance, for stimulus display, research practice has progressed from the use of light emitting diode (LED) arrays, to cathode ray tube (CRT) displays, and more recently to flat-screen liquid crystal displays (LCDs). Similarly, methods used in eye-tracking have included the use of magnetic field search coils, infrared reflectance, electro-oculography, and digital video techniques. In addition, experimental parameters such as the eccentricity of the target stimulus with respect to the fixation point vary between studies, often as the result of technical constraints (such as available display size) rather than as the result of specific theoretical motivations.

As Figure 2 seeks to highlight, a consequence of this variation in experimental method is that a "typical" study does not exist. In the current review, therefore, we wished to explore the possibility that such aspects of experimental design may have differentially affected the relative RTs of persons with PD and controls, and that the range of results previously reported might, in part, be explained by such differences in equipment and methodology. Specifically, we report two meta-analyses of results compiled from a systematic review of relevant studies. In the first, we used quantitative pooling to combine all previously reported effects in experiments involving visually-guided saccades, to see if there is an overall trend in RT differences. In the second, we used meta-regression to assess whether these RT differences are consistently related to identifiable aspects of experimental design that are known, or might be expected, to effect reaction times or its measurement.

Methods

Data sources and inclusion criteria

We performed a comprehensive literature search of Medline, SCOPUS and PsycINFO databases for relevant, full-length articles published up to the 21st of May 2007 using the search expression: *parkinson* AND ("eye movement" OR "ocular motor" OR "ocular movement" OR "oculomotor" OR "sensorimotor" OR "visual movement" OR "visual behaviour" OR "visual behavior" OR *saccad* OR "orienting" OR "overt attention" OR "covert attention" OR "spatial attention" OR "visual attention" OR "selective attention"). We also searched the bibliographies of reviews and of the articles identified by these searches, and consulted experts concerning other studies. Study inclusion criteria were: (i) published in English in a peer-reviewed journal or book, (ii) quantitative study of visually guided saccade dynamics in humans, (iii) patient group with idiopathic PD and no reported signs of dementia, (iv) age-matched control group of healthy subjects, (v) mean saccadic RTs reported for both groups. We excluded duplicate publications, i.e. studies with any overlapping patient populations from the same centre.

Data gathering

For each study we extracted the mean saccadic RT of the patient and control groups. The standard deviation (SD) of mean RT was also recorded, where available, as this is required to compute the weighting scheme used to compare studies. Where SD was not available a substitution method was used as described in Appendix 1 in the Electronic Supplement. Mean patient RT was subtracted from mean control RT to obtain our main outcome variable *difference in mean RT*, hence a positive value of this measure indicates shorter latency RTs for persons with PD compared to controls.

In studies that provided separate RTs for different subgroups of patients, we preferentially used data for patients off medication, otherwise we collapsed data across all subgroups (weighting by number of participants).

In addition to RT data, a range of parameters describing participant demographics, disease severity, experimental equipment and procedure, and data analysis methods were also extracted from each study as detailed in Appendix 3 in the Electronic Supplement. Prior to analysis, all variables were examined for accuracy of data entry, fit between their distributions and the assumptions of multivariate analysis, and missing values. In all cases tabulated data were used in preference to plotted data. We also attempted to contact the authors of all articles for which we had incomplete or potentially inaccurate data. Procedures used to extract the values of specific parameters are detailed in the relevant tables. Categorical variables were coded using the un-weighted effects method (Cohen et al., 2003). Parameters with more than 15% of values missing were excluded from the regression analysis, otherwise missing values were replaced using the mean of all values, or with the median for categorical variables.

Data Analysis

Quantitative pooling: Analyses were performed using Review Manager 5 (2007, The Cochrane Collaboration). Studies were weighted using the inverse variance method and overall effect computed using the random effects model (DerSimonian and Laird, 1986); effect sizes are reported in milliseconds together with their 95% confidence intervals. The Z score was used to test for overall effect and Chi square statistic to assess heterogeneity; both tests using an alpha level of 0.05. Additionally, separate

sub-group analyses were performed for results obtained using the *gap, step*, and *overlap* paradigms.

Meta-regression: Analyses were performed using the Lipsey/Wilson SPSS macro, METAREG (Lipsey and Wilson, 2001), using the same inverse variance weights as in the quantitative pooling analysis. Following the recommendations of Lipsey and Wilson (2001), a stepwise mixed-effects meta-regression was used, as detailed in Appendix 4 in the Electronic Supplement, to identify likely predictor variables on purely statistical grounds. Regression equations are reported for the final model, along with the R-squared statistic (equivalent to the percentage variance accounted for by the model), Q statistics (representing the total and residual variance explained by the model), and individual model coefficients (both standardised and unstandardised) with their corresponding p-values. Post-hoc tests, using a mixed effects model, were also performed to determine whether significant predictors of group differences are acting via their effect on the patient group, controls, or both.

Results

Evidence base

The literature search yielded 1529 references of which 627 (41%) were duplicates. Of the 902 unique articles, 811 (90%) were classified as failing to meet the inclusion criteria based on title and/or abstract, and a further 51 (5.7%) based on inspection of the full text. Of the remaining 40 articles, several contributed more than one eligible study (since results from more than one visually-guided paradigm were reported

independently). In all, therefore, the literature search yielded 47 studies containing data on 542 PD patients (mean 14.2 per study) and 434 controls (mean 11.8), of which 27 studies reported results for the step paradigm, 11 for the gap paradigm, and 9 for the overlap paradigm. Of the 47 studies, 41 provided both the mean saccadic RT and its SD (or the standard error from which SD was directly estimated). For the remaining 6 studies, which provided only the mean RT, the SD was estimated from the reported p-value for 3 studies by assuming that the p-values were quoted for Student's t-distribution (see Supplementary material). For the remaining three studies the SD was estimated with the mean standard deviation of those studies that reported it directly.

In total, 23 independent variables (IVs) were recorded for each study, 15 continuous and 8 categorical. All 8 of the categorical variables had less than 15% missing values, but this was only true of 3 continuous variables, meaning that the remaining 12 were excluded from the study (see Appendix 3 in the Electronic Supplement for details). This left the eleven predictor variables listed in Table 1, each of which can be classified, according to the scheme in Figure 2, as having a possible impact on saccadic RTs through either the stimulation, participant selection, or measurement aspects of the experimental design.

Table 1. Predictor variables used in the meta-regression analysis classified according to experimental design category (see Figure 2). Sub-classes are shown for categorical variables and range for continuous variables. Details of how each variable was extracted together with additional descriptive statistics are given in Appendix 3 in the Electronic Supplement.

Stimulation:

Experimental paradigm for stimulus timing (gap, overlap, step)

Mean eccentricity of target (mean range 4 to 40 degrees)*

Number of possible target positions (two, not two)*

Fixation stimulus type (central, roaming)*

Different trial types interleaved (yes, no)

Audible trigger cue (present, absent)

Participant selection:

Average age of PD group (range 52.5 to 76.9 years)

Difference in mean ages of PD and control group (range -12.3 to 3.7 years)*

Measurement:

Display equipment type (CRT, projected spot, LED)*

Tracking equipment type (infrared, electro-oculography, search coil or video)

Short latency saccades discarded (yes, no)*

Quantitative Pooling

Forrest plots summarising the overall and sub-group results are shown in Figure 3. Of the 47 studies, 41 provided both the mean saccadic RT and its SD (or the standard error from which SD was directly estimated), for the remaining 6 studies, which provided only the mean, the SD was estimated from the reported p-value for 3 studies by assuming that the p-values were quoted for Student's t-distribution (see Supplementary material), and the remaining three were replaced with the mean standard deviation. The overall effect of PD was found to be a significant increase in RT, with a weighted difference in mean RT of -19.44 ± 9.78 ms ($Z= 3.90$, $p<0.0001$), but with significant heterogeneity ($\chi^2=157.13$, $p<0.00001$, $I^2= 71\%$). Here heterogeneity analysis tests the assumption that all of the effect sizes are estimating the same population mean. The significant outcome indicates variability across effect sizes exceeding that expected from sampling error alone, from which we can infer that there are important between-study differences. One obvious candidate for such differences is the type of visually-guided paradigm used (step, gap, or overlap). Analysis by paradigm sub-group showed a significant difference in mean RTs for step (-26.46 ± 11.75 ms; $Z= 4.42$, $p<0.00001$) but not for either gap (-11.30 ± 17.86 ms; $Z= 1.24$, $p= 0.21$) or overlap (-2.43 ± 33.73 ms; $Z= 0.14$, $p=0.89$). Heterogeneity was found to be significant for all three paradigm sub-groups (step: $\chi^2 = 88.52$, $p< 0.00001$, $I^2= 71\%$; gap: $\chi2 = 22.15$, $p=0.01$, $I^2= 55\%$; overlap: $\chi^2 = 37.14$, $p< 0.0001$, $I^2= 78\%$). From this we can conclude that variation in effect sizes is not solely attributable to differences in the type of paradigm used. In summary, the results of the quantitative pooling analysis show an effect of slowed response time in PD that is strongest in the step paradigm, weaker in the gap paradigm, and negligible in the overlap paradigm. Moreover, our heterogeneity analyses imply a potentially more

complex relationship between PD and visually-guided saccadic RT that may be due to other sources of variation between studies.

Meta-regression

Main analysis: Difference in mean RT was regressed against the eleven potential predictor variables using a mixed effects model, as detailed in Appendix 4 in the Electronic Supplement, with the step-wise procedure identifying four significant predictor variables in the following order: mean target eccentricity ($p= 0.001$), difference in mean age ($p= 0.001$), tracking equipment type ($p= 0.001$), and display equipment type ($p= 0.012$). Model Q was significant ($Q= 52.5$, $p< 0.0001$), indicating that the regression model explained a significant portion of the variability in difference in mean RTs ($R^2=0.52$). Residual Q was non-significant ($Q= 49.1$, $p> 0.05$), as by assumption for a mixed effects model it is composed entirely of sampling error and random variation. The coefficients of the predictive model are as shown in Equation 1:

Difference in mean RT	=	-2.03	×	mean target eccentricity (degrees)	(1)
		+4.85	×	difference in mean age (years)	
		-20.61	×	tracking equipment type (other=-1; electro-ocular=0; infrared= +1)	
		+12.79	×	display equipment type (LED=-1; projected spot=0; CRT=+1)	
		+27.17			

Partial regression bubble plots are shown in Figure 4 to illustrate the relationship between the difference in mean RT and each of the predictor variables. This type of plot illustrates the individual contribution of a predictor after the other predictors in the model have been controlled for. Hence, the axis scales represent residual values, generated using the method described in Appendix 4 in the Electronic Supplement,

and not the original parameter values[1]. The line of best fit has a slope equal to the unstandardised regression coefficient of the plotted predictor.

Target eccentricities used in the collected studies ranged from 4 to 40 degrees, and so the first component of the model suggests that, if one were to perform a controlled experiment in which target eccentricity is systematically varied between these two values, the observed difference in mean RTs between persons with PD and controls might change by up to 73 ms (2.03×(40 - 4)). More specifically, Equation 1 shows that mean target eccentricity interacts with PD such that patients generate faster RTs than controls at small eccentricities, slower RTs for large eccentricities, and similar RTs at some intermediate value (Figure 4A). Difference in the mean ages of the control and patient groups ranged from -12.30 to +3.66 years in the studies analysed. The model predicts that experiments conducted using differences at the extremes of this range might observe a 77 ms (4.85×(3.66 + 12.30)) difference in RT due to this variable alone (Figure 4B). The third and fourth components of the model indicate that choice of tracking and display equipment can change the measured difference in mean RT by up to 41.22 ms (2 x 20.61) and 25.58 ms (2 x 12.79) respectively (Figures 4C & 4D).

The experimental setup most frequently used in the collected studies employs electro-oculography eye-tracking equipment and an LED display. Substituting appropriate values into Equation 1 (0 for tracking equipment type, -1 for display equipment type,

[1] Note that since the outcome variable depends on multiple predictor variables, the correlation between it and any single predictor is often obscured by the ”noise” caused by the other predictors. Hence it is not appropriate to plot the predictor and outcome variables in their original units.

and 0 for difference in mean age i.e. perfect matching) and solving for a zero difference in mean RT gives a crossing point of 7.1 degrees. In other words, PD patients should be faster than controls at target eccentricities below 7.1 degrees and slower above this level. A similar prediction can be obtained by inference: all studies with a mean target eccentricity of 6 degrees or less report that PD patients are faster to react than controls. Similarly, no study reports that PD patients are faster than controls for eccentricities of 26 degrees or more. If the crossing point, at which PD patients and controls have the same RT, lies midway between these two values one would expect zero mean reaction time difference at the higher threshold of 16 degrees ($6 + (26 - 6)/2$).

Post-hoc tests

We next performed post-hoc tests, using mixed effects meta-regression to examine whether the 4 identified predictor variables produced the difference in mean RT via their effect on one or both groups. For both PD and control groups, neither overall model fit, nor any coefficients were significant ($p > 0.05$), meaning that our best approximation of the mean RT of each group, based upon these predictors, is simply the weighted mean value for all studies: 267 milliseconds for persons with PD and 249 milliseconds for controls.

Discussion

This is the first systematic review and meta-analysis of the literature concerning the effects of PD on response times for visually-guided saccades. Our principal result is to

have demonstrated, using meta-regression, that several experimental parameters have substantial effects on study outcome that can account, collectively, for 52% of the observed variance in mean RT difference in the studies surveyed. This result would appear to explain why the mean RTs of individuals with PD are sometimes reported as being shorter, and sometimes as longer, than those of age-matched controls. It would seem that, by pure coincidence, the range of experimental parameters used in studies to date are such that positive and negative differences in mean RT have partly cancelled to leave only a relatively small aggregate effect, as demonstrated by our quantitative pooling analysis. Whilst the heterogeneity of previous results has led some authors to conclude that there is little or no effect of PD upon reflexive saccades, the pattern revealed by the current analysis implies, instead, that predictable and consistent effects of PD should be demonstrable when these design parameters are taken into account.

How experimental parameters might give rise to differences in mean RT

We now consider, in more detail, relationships between specific experimental parameters and differences in mean RT (as previously summarised in Figure 2), and propose that these relationships are due to either:

- genuine differences in RT resulting from differential oculomotor function in persons with PD compared to controls;
- differences in measured RT, but *not* in the underlying actual RT, due to PD symptoms, oculomotor or otherwise;
- genuine differences in RT due to differences between participants groups that are unrelated to disease state.

After describing these categories of effects we then discuss possible neurological causes for those differences that are likely to be due to PD-related changes in oculomotor function, before briefly discussing some of the limitations of the current study.

Genuine differences in RT due to differential oculomotor function in PD: sensitivity to stimulus eccentricity

We have demonstrated that mean target eccentricity is significantly predictive of the mean RT difference between patient and control groups. Those experiments that presented targets *predominantly* in the peripheral visual field were more likely to find that PD patients have slower RTs than controls, while those that mainly presented targets closer to the fovea found that PD patients have faster RTs.

It is reasonable to suppose that this finding is due to a genuine abnormality in patient brain function, as stimulus eccentricity is known to have a significant effect on the RTs of healthy subjects. Specifically, when a target of a fixed size is presented to a healthy individual at various eccentricities, the function describing their saccadic mean RT with respect to eccentricity is bowl-shaped (see Figure 5), with RTs to small (< 5 degree) and large (> 20 degree) target eccentricities significantly longer than those to mid-sized target eccentricities (*Small*: Kalesnykas and Hallett, 1994; Wyman and Steinman, 1973. *Mid-sized*: Cohen and Ross, 1977; Heywood and Churcher, 1980). *Large*: Bartz, 1962; Kalesnykas and Hallett, 1994; Zambarbieri et al., 1995).

Our analysis compares mean RT to the aggregate variable of *mean* target eccentricity, as opposed to that of *actual* target eccentricity. This means that we cannot directly

compute the predicted bowl-shaped relationship between eccentricity and RT, or show how this might be altered in PD. Notwithstanding this, our results do strongly suggest that PD patients have an abnormal response to target eccentricity that could be demonstrated in a suitably controlled experiment. Specifically, based on our findings, we predict that such an experiment would find that patients, when compared to controls, have a shorter RT to low eccentricity targets and a longer RT to high eccentricity targets, as illustrated in Figure 5. That the difference in mean RT is strongly sensitive to eccentricity could help resolve the controversy as to why the saccades of PD patients have been found to be "hyper-reflexive" in some studies (e.g. Briand et al., 2001, Kingstone et al., 2002) but not in most others (as summarised in Figure 3).

Genuine differences in RT due to differential oculomotor function in PD: sensitivity to display properties

PD-related changes in oculomotor function might also account for our finding that the type of display technology used by an experimenter is predictive of RT difference. We found that PD patients are more likely to show a prolonged RT compared to controls if LEDs were used as opposed to a CRT display. It may be that this is related to the brightness, contrast ratio, or colour of the stimuli typically produced using these technologies, to which persons with PD may show differential sensitivity (see below). Alternatively, the angle subtended by displayed stimuli may vary systematically with display type (we did collect data on this, but generally it was poorly reported). LED displays are commonly constructed in an arc around the subject so that both the angle subtended by a stimulus, and the vergence and accommodation required to focus upon it, remain roughly constant irrespective of target eccentricity. CRTs, by contrast, are

essentially flat, so that a stimulus of a fixed size on the screen (as commonly used) will subtend a smaller angle when presented in the periphery because it is further from the subject's eye. For the same reason, targets displayed on a CRT will also require different accommodation and vergence depending on their location. All of these properties are known to modulate saccadic RTs in healthy subjects (see Leigh and Zee, 2006, for review). While it is impossible to identify from the current study which, if any, of these differences might underlie an effect of display type on the difference in mean RT, this finding is sufficient to warrant caution in directly comparing the results of studies that use fundamentally different display apparatus.

Differences in measured RT, but not in the underlying actual RT, due to PD symptoms

Upon first consideration, it seems rather odd that an experimenter's choice of eye tracking equipment should in any way affect the difference between results for PD patients and controls, as measurement is a passive activity by definition. Nonetheless, we found that PD patients are more likely to display slower mean RTs when infrared tracking is used instead of video or search coil methods. We suggest that this does not represent a real change in RT, but rather a measurement effect that is greater in one group than the other.

One prospective source of measurement effect relates to the way in which a saccade is determined to have started. The most common way of doing this is to use a velocity criterion whereby a saccade is deemed to have started once the eye's velocity rises above a certain threshold velocity. The saccades of PD patients have been found to exhibit more damping than those of age-matched controls (Chen et al., 1998) with the

consequence that the eye accelerates less vigorously. As a result of this, the saccades of PD patients will typically take slightly longer to cross a velocity threshold even if their true RT is identical to that of controls. In keeping with the findings of our study, this artificial prolongation of measured RT in PD patients is likely to be more pronounced in studies employing infrared tracking, as higher velocity thresholds are more commonly used with this method as compared to other technologies.

Another potential source of a measurement effect relates to the finding that PD patients blink less than healthy individuals (Biousse et al., 2004). Infrared tracking equipment calculates eye position based upon the amount of light reflected back from a subject's eye, and when a subject blinks the recorded reduction in reflectance can be mistaken for a saccade onset by analysis software (or a human analyst). If a blink occurs just prior to a genuine saccade, it is possible that the saccadic latency for that trial will be erroneously recorded as being shorter than it actually was. Since PD patients blink less frequently than controls, fewer of their saccades will be affected in this way, so that their mean RTs will appear slightly extended compared to controls. If other tracking systems are less susceptible to this error then this provides a second possible contributor to the effect of tracking equipment type on the measured difference in mean RT.

Genuine differences in RT due to differences between participants groups unrelated to disease state

Given the well documented finding that the mean saccadic RT of healthy individuals increases as they age (Pitt and Rawles, 1988; Sharpe and Zackon, 1987), our finding that a patient group, with a mean age lower than that of the control group, is more

likely to display a reduced saccadic latency, is hardly surprising. We propose that this finding in no way relates to the disease state of the patient group, but rather serves to highlight the importance of properly controlling for known moderators when conducting research of this type.

Possible neurological causes for differences in visually-guided saccadic RT

We noted above that the effects of both target eccentricity and stimulus display technology could be due to differential oculomotor function in persons with PD compared to controls. In the following we focus on the eccentricity effects as the theoretically more important of these two findings, however, it is worth noting that the effect of display apparatus might also be explained by some of the PD-induced changes in perceptual processing considered below.

In considering how processing of stimuli at different visual angles might be altered in PD it is useful to think about why the bowl-shaped eccentricity function, described above (Figure 5), occurs in normal subjects. We suggest that a number of distinct mechanisms may contribute to the elevated RTs observed for peripheral and peri-foveal stimuli, as compared with stimuli of medium eccentricity, and discuss how these mechanisms may map onto the perceptual, executive, and motor areas within the oculomotor system. We also discuss how processing in each of these areas may be affected by PD in order to explain why target eccentricity has a different effect on persons with PD compared to controls.

Perceptual mechanisms

First, the non-linear fashion in which visual space is represented throughout the oculomotor system may partly account for the increase in RT to *peripheral* stimuli. Specifically, the central visual field is represented over a larger area of neural real-estate than the periphery. This is observed in areas of cortex (Azzopardi and Cowey, 1993), where it is referred to as "cortical magnification", and in sub-cortical structures like the superior colliculus (SC) (Robinson, 1972). It seems likely that this diminished representation of the periphery means that the initial neural response elicited by the onset of a peripheral stimulus will be smaller than that elicited by an identical stimulus presented at a less eccentric location, and that this smaller initial response is, in turn, responsible for the prolonged RT.

Second, the existence of surround inhibition in the retina (Bodis-Wollner, 1990) and in the superficial layers of the SC (Moors and Vendrik, 1979) may explain why RTs are relatively prolonged for *peri-foveal* targets. In the superficial SC, for instance, when the size of a stimulus presented at a particular location is systematically increased, the magnitude of the neural response elicited remains constant (or increases slightly) until a critical stimulus size is reached beyond which the elicited neural response actually starts to diminish. In the SC, the critical stimulus size varies with eccentricity so that in the periphery the surround inhibition is only activated for relatively large stimuli (Goldberg and Wurtz, 1972). Given the small point-like stimuli commonly used in oculomotor studies, the inhibitory surround is unlikely to be triggered for peripheral presentations, but for presentations close to fovea it is possible that the surround is activated causing attenuation of the initial neural response for that eccentricity and, in turn, a prolonged RT.

Changes in PD

If the above mechanisms contribute to the bowl-shaped eccentricity function in normal subjects, how might they be disrupted in persons with PD? First, it is known that the loss of dopamine (DA) producing cells that characterises PD affects retinal processing (Bodis-Wollner, 1990), with consequences including abnormal spatial and temporal contrast sensitivity and colour discrimination (Rodnitzky, 1998). In particular, Bodis-Wollner (1990) suggests that altered contrast sensitivity may arise due to reduced efficiency of centre-surround circuitry in the retina. If the inhibitory surround, in retina and downstream structures, is reduced in PD this could help to explain why patients respond to peri-foveal stimuli faster than controls. Second, if DA has a general enabling function in the retina, it is likely that the under-represented periphery would also be the first to be affected by any reduction in tonic DA levels, perhaps explaining why persons with PD exhibit prolonged RTs in response to peripheral stimuli.

Executive mechanisms

It has been proposed that the circuitry of the basal ganglia (BG) fulfill an important role in arbitrating between incompatible action representations, with BG output, from the substantia nigra pars reticulata (SNr), communicating the outcome to downstream structures (e.g. Mink, 1996; Redgrave et al., 1999). In particular, SNr sends inhibitory output to both the SC and to regions of thalamus that are reciprocally connected to the frontal eye fields (FEF), leading to the suggestion that the BG act to gate potential saccadic commands sent to striatum from SC and the FEF (Hikosaka et al., 2000). Additionally, there is evidence to suggest that within the SC, fixation and target

related activity is mutually exclusive (Dorris et al., 1997), so that a saccade cannot be initiated until fixation activity has diminished sufficiently. This suggests the existence of competitive dynamics within the SC that is modulated by BG output.

Changes in PD

It is commonly accepted that the loss of dopaminergic input to the BG is one of the principal causes of motor symptoms in persons with PD (Zigmond, 2002). As we have demonstrated in our own models of these nuclei (Gurney et al., 2001, 2004), a reduction in tonic DA levels can result in elevated levels of activity in the SNr and reduced efficiency of BG gating of motor acts. There is good evidence from studies with primates that increased SNr output leads to an increase in saccadic RT (Hikosaka et al., 2000), consistent with the overall finding of the current study that reflexive saccades are somewhat slower in PD. That this increase in saccadic RT is exaggerated for peripheral targets may be a consequence of the additional inhibitory output from SNr having a disproportionate effect on the already diminished representation of such stimuli that arises due to "cortical magnification" as discussed above.

Increased SNr output in PD may also disrupt the arbitration process between the fixation and target stimuli. Specifically, increased inhibition of the SC could cause fixation activity to decay more rapidly once the fixation stimulus is extinguished so that it competes less with burgeoning target-related activity, allowing the latter to evolve more rapidly. This change in the competitive dynamics could improve response times in PD, for small eccentricities, at the cost of robust fixation. It is notable, in this regard, that our sub-group analysis showed a negligible difference in mean RT for persons with PD compared to controls in the *overlap* paradigm. In this

experimental design the fixation light remains on after target onset, a situation that could be expected to lead to more prolonged competition between the two stimuli. Under these circumstances, the improvement in RT due to the changed competitive dynamics in PD may be sufficient to counter-balance the negative effect of PD on response times for targets are larger eccentricities; resulting in a net difference in mean RT that is close to zero. A full exploration of the potential consequences of altered BG output in PD will, we believe, require computational modeling of the oculomotor circuit and of the impact of disease-related changes on its various components.

Motor mechanisms

Recent insights into the pathology of PD suggest that significant damage to midbrain dopamine cells may only occur at a relatively advanced stage of the disease (Braak et al., 2003). Proteinaceous inclusion bodies—which are predictive of progressive cell loss in PD—have been observed to spread from the vagus nerve to the medulla oblongata and pontine tegmentum before reaching the midbrain (Braak et al., 2006). Thus, by the time patients start to show early signs of cell loss in the midbrain, the damage to affected areas of the brainstem is in an advanced stage. As a result it is possible that cell loss within the brainstem's saccadic generator circuit may account for abnormal RTs in patients, although it is unclear why this would differentially affect movements to different eccentricities.

Limitations of the present study

A meta-analysis of the impact of PD on reflexive saccades should ideally take into account measures of disease severity and of patient medication. Unfortunately

relevant details were not reported with sufficient frequency in the studies surveyed to be included in our regression analysis. Furthermore, concerning disease severity, in addition to sparse reporting, there was also inconsistency in the measurement scale used; the majority of studies scored patients on the Hoehn and Yahr (1967) scale, but a significant minority used the UPDRS scale (Fahn and Elton, 1987). This shortfall in data prevented us from investigating the extent to which the predictions made in this study hold true for patients at different stages of the disease. It also meant that we are unable to evaluate whether existing treatments have an impact on the visually-guided saccadic response times of persons with PD. As a general proviso, it is also important to note that likely relationships between aspects of experimental design and differences in RT, identified through meta-regression, cannot be demonstrated to be causal by this procedure; direct evidence for the proposed relationships must await the outcome of appropriately designed experiments.

Conclusion

This study has demonstrated that amongst the heterogeneous findings of 47 studies, conducted over more than 3 decades, there lay hidden results, and as such it serves as a demonstration of the utility of meta-regression in the field of psychophysics. Of these new insights, those relating to equipment choice and subject selection highlight the possible impact that the experimenter's design decisions can have upon a study's outcome, and suggest that caution is needed when comparing seemingly identical experiments.

That PD patients demonstrate a reduced responsiveness to peripheral events is one of our most significant findings, as it may impact upon their quality of life. Persons with PD will respond significantly more slowly to salient stimuli in their peripheral field of view adding to a vulnerability that is already increased by their reduced motoric capacity. Likewise our results are consistent with earlier findings that PD patients can generate faster, or "hyper-reflexive", saccades (see Briand et al, 2001; Kennard et al., 2002) though only to targets at small eccentricities. This trait could make PD sufferers more distractible by peri-foveal stimuli leading to difficulty in maintaining fixation during tasks that require focused visual attention. We feel that these findings warrant further study through a controlled experiment designed specifically to investigate the relationship between RT and target eccentricity in PD. If patients in the early stages of the disease are shown to display these eccentricity effects, then it is also possible that such experiments might also provide the basis for a novel PD screening technique. Finally, given the likely role of the BG in oculomotor decision making, further study of abnormal eye movements in PD may also provide us with a window on the role that these nuclei play in executive function.

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Figure Legends

Figure 1. Basic experimental procedure for visually-guided saccade paradigm, showing gap, step and overlap variants. Abbreviations: F, fixation stimulus; T, target stimulus; RT, response time; e, angular target eccentricity.

Figure 2. A framework for identifying experimental properties affecting the findings of comparative studies of visually-guided saccades. Important elements of experimental design include the visual, spatial and temporal aspects of the *stimulation* protocol employed, *participant selection,* and the choice of *measurement* equipment. Differences in response time, under different experimental designs, might then arise due to PD-induced changes in the *oculomotor system***,** that directly affect saccade generation or its measurement, or changes in *non-oculomotor systems* that have an indirect effects on saccade control or on the detection of eye movements by different equipment types. Reaction time differences might also be introduced if *participant selection* leads to patient and control groups that differ along any dimension affecting saccadic latencies other than disease state. Abbreviations: SC, superior colliculus; LIP, lateral intraparietal sulcus; FEF, frontal eye field; BG, basal ganglia; SG, saccadic generator circuit.

Figure 3. Forest plot showing weighted mean difference (WMD) in RT between controls and persons with PD, and its 95% confidence interval, for all 47 studies surveyed. Results are grouped according to the temporal overlap paradigm used (gap, overlap, or step) with overall effects shown for each sub-group and for the full sample. Mean saccadic latency is shorter for controls overall (-19.44 ms), but sub-group analysis shows that this is most pronounced in the step paradigm (-26.46 ms),

weaker in the gap paradigm (-11.30 ms) and almost negligible in the overlap (-2.43 ms) paradigm. Moreover, there is significant heterogeneity between studies both overall, and within each experimental paradigm, implying that additional between-study differences make a significant contribution to the observed variance.

Figure 4. Partial regression bubble plots for difference in mean RT (y-axis). A) mean target eccentricity, B) difference in mean age, C) tracking equipment used, D) display equipment used. Note axis scales represent residual values, and bubble size the relative weight used for each study. The plots show that these experimental design parameters interact with disease state such that persons with PD may generate shorter, similar, or longer latency RTs than controls depending on the specific design used.

Figure 5. Stylized representation of the 'bowl-shaped' relationship between response time (RT) and target eccentricity. Solid line represents data for normal subjects. Broken line represents *predicted* data for PD patients.

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