



The influence of motor and cognitive impairment upon visually-guided saccades in Parkinson's disease

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ABSTRACT

Studies of saccades in Parkinson's disease (PD) have seldom examined the influence of cognitive status, ranging from normal cognition, through mild cognitive impairment, to dementia. In a large and heterogeneous sample, we examined how motor and cognitive impairment was reflected in the performance of reflexive, visually-guided saccades. We examined 163 people with PD and 47 similar-aged controls. Ninety three of the PD group had normal cognition (PDN), 48 had mild cognitive impairment (PD-MCI), and 22 had dementia (PDD). Pseudo-random targets (amplitudes of 5, 10, 15 and 20 deg and inter-stimulus-intervals ranging from 550 to 1800 ms) were shown in 108 mixed randomised trials, incorporating gap, step, and overlap onset conditions. Analyses were conducted using multi-level regression modeling. Participants were first assessed by continuous measures (Unified PD Rating Scale motor score and the Montreal Cognitive Assessment). Prolonged latency was significantly related to both motor and cognitive impairment, with the cognitive effect being compounded by increasing age. Decreased saccade amplitude, meanwhile, was primarily related to motor impairment. When assessed by discrete cognitive categories, all of the PD groups showed reduced saccadic amplitude relative to controls. Saccadic latencies, meanwhile, were abnormally prolonged only in the PD-MCI and PDD groups (the control and PDN groups were similar to each other). Latency in the overlap task was particularly sensitive to increasing motor and cognitive impairment. We conclude that reflexive saccades in PD are subtly decreased in amplitude even early in the disease process. Prolonged saccade latency, meanwhile, tends to occur later in the disease process, in the presence of more substantial motor and cognitive impairment, and greater age. The progressive impairment of reflexive saccades, and the differential onset of amplitude and latency impairments, may make them a useful objective tool for assessing disease status.

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1. Introduction

Fast gaze-shifting eye movements (saccades) have been studied extensively in Parkinson's disease (PD). The decreased amplitude of saccades mirrors the hypokinesia of other motor systems, which is the hallmark of the disease (MacAskill, Anderson, & Jones, 2002). As with other motor deficits, saccadic impairments in PD are task-dependent. Simple reflexive saccades in response to a suddenly appearing target have often been reported as unaffected (for example, Crevits, Vandierendonck,

Stuyven, Verschaete, & Wildenbeest, 2004; Tanyeri, Lueck, & Kennard, 1989). In contrast, impairments are pronounced when higher-level voluntary control is involved, such as when the movement is guided by memory, by a learned rhythmic pattern, or when it must be sent in the opposite direction (an 'anti-saccade') to a visual target (Kimmig, Hausmann, Mergner, & Lücking, 2002; Le Heron, MacAskill, & Anderson, 2005; O'Sullivan et al., 1997; van Stockum, MacAskill, Anderson, & Dalrymple-Alford, 2008).

Despite the resulting emphasis on voluntary saccades in PD, the assessment of reflexive saccades has been revisited recently (Chambers & Prescott, 2010; Terao et al., 2011). Chambers and Prescott's meta-analysis showed that across 47 conflicting studies, there was overall evidence of slightly prolonged reflexive saccade latency in PD. The difference was most consistent in the 'step' task,

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in which a peripheral target appears at the same moment as the currently-fixated target disappears. The difference was not significant when the two events were separated temporally (the 'gap' task) or when the onset of the peripheral target preceded the offset of the fixation point (the 'overlap' task). They attributed much of the variation across studies to methodological issues, such as target eccentricity, patient age, and to certain types of eye tracking and display technologies. Meta-analyses are valuable but limited by inconsistencies in methodology and data reporting across component studies. For example, Chambers and Prescott could not meaningfully assess the effect of disease severity as, when reported, these measures were generally collapsed across the entire sample (with a mean of only 14 patients and 12 controls in each study).

A recent investigation by Terao et al. (2011) addressed this, with their large sample of 66 patients and 87 controls allowing for a meaningful consideration of the effect of (motor) disease severity. They showed that impairment of memory-guided saccades generally occurred early in the disease and increased progressively with Hoehn and Yahr disease stage. Reflexive saccades, however, did not show uniform deterioration. Reflexive saccade amplitude was reduced in the early stage of motor impairment but did not continue to decrease thereafter. Reflexive latency, meanwhile, was unaffected at Hoehn and Yahr Stage 1, became prolonged significantly at Stage 2, and did not deteriorate thereafter. By contrast, Mosimann et al. (2005) reported that both latency and gain of reflexive saccades was significantly worse in a group with Parkinson's disease dementia (PDD) compared to PD without dementia. It is increasingly recognised that cognitive deterioration is a common and important aspect of PD, with up to 80% eventually developing dementia (Aarsland, Andersen, Larsen, Lolk, & Kragh-Sorensen, 2003). Given the tight linkage between oculomotor control and attentional, memory and visuospatial processes, one might expect progressive saccadic impairment to accompany neuropsychological deterioration. The lack of progressive impairment of reflexive saccades seen by Terao et al. therefore might reflect their exclusion of patients with significant cognitive impairment (Mini Mental Status Exam score < 25). Studies other than Mosimann's have excluded PD participants with evidence of dementia, but many are likely to have included a proportion with mild cognitive impairment (PD-MCI). Patients with PD-MCI have measurable deficits in one or more cognitive domains including memory, attention, executive functioning, and visuospatial perception (Dalrymple-Alford et al., 2011; Goldman, Weis, Stebbins, Bernard, & Goetz, 2012), but unlike patients with PDD, they remain able to perform adequately in activities of daily living. Agreed criteria for the diagnosis of PD-MCI are only now being adopted (Litvan et al., 2012). Therefore, a portion of the unexplained variation across studies noted by Chambers and Prescott (2010) might be accounted for by the recruitment of differing numbers of participants with undetected PD-MCI.

In summary, Terao et al. (2011) demonstrated the influence of the degree of motor impairment upon reflexive saccade performance in Parkinson's, but excluded patients with substantial cognitive impairment. Mosimann et al. (2005) examined the influence of the extremes of cognitive status (patients who were unimpaired compared to those with dementia) but did not assess the role of motor status. We hypothesised that the two factors (cognitive and motor impairment) might independently influence aspects of saccadic performance. If so, then measurement of saccades might be an objective biomarker which is differentially sensitive to both facets of the disease.

We therefore present a study of reflexive saccades in Parkinson's disease using the largest patient sample to date, covering a wide range of severity in both motor and cognitive impairment. For the first time in a saccadic study, each patient underwent comprehensive neuropsychological testing and was then categorised using established criteria (Dalrymple-Alford et al., 2011; Litvan et al., 2012) as being either in the normal range or as having PD-MCI or PDD. We hypothesised that reflexive saccade amplitude would be subtly reduced even early in the course of the disease and should deteriorate further with increasing motor impairment. Reflexive latency, meanwhile, should be relatively normal in patients with intact cognition but become progressively prolonged in those with cognitive impairment. Such findings would suggest that these two reflexive saccade parameters might be faithful markers of PD motor and cognitive status, respectively, and therefore potential biomarkers for tracking disease progression and patients' response to putative neuro-protective or neuro-restorative therapies.

2. Material and methods

2.1. Subjects

A convenience sample of 163 PD participants was recruited from the Movement Disorders Clinic at the New Zealand Brain Research Institute, Christchurch, New Zealand. A movement disorders specialist (TJA) confirmed that subjects met the UK Parkinson's Disease Society's criteria for idiopathic PD (Hughes, Daniel, Kilford, & Lees, 1992). Forty seven healthy control subjects were recruited, matched for mean age and years of education. Exclusion criteria were previous history of other neurological, psychological or medical conditions, including atypical Parkinson's disease; moderate or severe head injury, stroke, major depression or learning disability; a history of cranial neurosurgery; major heart disease; diabetes requiring insulin; medication other than PD treatment known to have a significant effect on the CNS; alcohol abuse; and corrected visual acuity worse than 6/12 in the best eye. The study was approved by the Upper South A Ethics Committee of the New Zealand Ministry of Health. All subjects gave written consent and caregivers provided additional consent for participants with cognitive impairment.

PD patients were classified as having normal cognition (PDN, $n=93$), mild cognitive impairment (PD-MCI, $n=48$) and dementia (PDD, $n=22$) (Table 1). Our classifications were consistent with the Movement Disorders Society Task Force

Table 1
Clinical and demographic characteristics of the sub-groups.

	Controls $n=47$	PDN $n=93$	PD-MCI $n=48$	PDD $n=22$
Age	67.2 (9.9)	64.9 (8.6)	69.3 (8.0)	72.8 (7.0)
Sex ratio (M:F)	32:15	62:31	30:18	18:4
Years of education	13.7 (2.9)	13.0 (2.9)	12.6 (2.8)	12.8 (3.0)
WTAR (Premorbid IQ)	112 (9.5)	112 (8.0)	108 (9.9)	108 (11.1)
MMSE	29.0 (1.0)	28.9 (1.1)	27.3 (2.0)	23.9 (3.0)
MoCA	27.2 (1.9)	26.5 (2.2)	23.5 (2.6)	17.2 (4.1)
PD duration		4.8 (4.1)	6.9 (4.5)	12.2 (8.2)
UPDRS III		23.9 (13.5)	29.8 (14.3)	48.5 (20.3)
Hoehn & Yahr		1.9 [1–4]	2.4 [1–4]	3.3 [2–4]

Values in round brackets=SD, square brackets=ranges. PDN=PD with normal cognition, PD-MCI=PD with mild cognitive impairment, PDD=PD with dementia.

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