Eye movement control and cognition in Parkinson's disease

Saskia van Stockum

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Abstract

Many studies have found evidence of abnormal eye movement control in Parkinson's disease. Deficits in the inhibition of unintended saccades and slowed initiation of intentional saccades have been reported in some, but not all, investigations. Also over recent years the presence of cognitive impairment in a proportion of patients with Parkinson's disease has been highlighted. Efficient use of working memory resources is thought to be involved in the performance of tasks in both domains. With a comprehensive selection of saccadic and neuropsychological tasks, the current study investigated whether aspects of abnormal oculomotor control are associated with impairment of cognitive functions.

Nineteen Parkinson's disease patients and eighteen healthy age matched control subjects performed six eye movement tasks and completed a neuropsychological test battery assessing five different aspects of cognitive functioning. Deficits were found in both the oculomotor and the cognitive domain in the group of patients.

As a group, the patients made more reflexive errors in antisaccade tasks, more inhibition errors in a delayed response task, and were slower to initiate intentional saccades. The three measures of abnormal oculomotor control were not consistently associated with cognitive impairments or with each other. Longer latencies of correct antisaccades and increased number of errors in a delayed response task were associated with lower scores in different cognitive tests. Reflexive errors in the antisaccade task were not associated with cognitive deficits, but with the tendency to produce very fast visually triggered responses. The results suggest that, at least in Parkinson's disease, different neural mechanisms may be involved in specific aspects of abnormal oculomotor control.

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Table of contents

1 Introduction

1.1 General overview

The study of eye movement control has become a valuable research tool as the neural mechanisms underlying oculomotor functions are now relatively well understood (Hikosaka et al., 2000; Leigh & Kennard, 2004; Munoz & Fecteau, 2002). Abnormal eye movement control has been found in a wide range of neurological and psychiatric conditions, especially those with pathology of the frontal lobes or basal ganglia. Of particular relevance to the current study are investigations of horizontal saccades (fast eye movements) in Parkinson's disease (PD). Several studies report evidence for abnormal saccade production in PD patients. However, so far the evidence has not provided a clear picture of the effects of PD on eye movement control.

The cardinal motor symptoms of PD are a result of depleted nigrostriatal dopamine transmission and associated basal ganglia (BG) dysfunction. In addition to overt motor symptoms (including bradykinesia, tremor and/or rigidity) PD patients may suffer mild to serious cognitive impairment. Some investigators have estimated that cognitive decline may progress through to dementia in 20 - 80% of these patients (McKeith, 2004).

Nearly all studies of oculomotor control in PD have compared groups of non-demented PD patients and healthy subjects of similar age and background. Some, but not all, investigations of oculomotor function have found deficits of control or significantly slowed responses associated with PD. Only one study compared oculomotor control in a group of non-demented PD patients and a group of clearly dementing PD patients (PD-D) with a group of healthy control subjects. That study (Mosimann et al., 2005) found differences between the PD-D group and the healthy control group, while eye movements in the non-demented PD group did not differ from those of the healthy subjects.

Cognitive processes are involved in the efficient performance of many of the tasks used to assess oculomotor function. Most previous studies investigated eye movements in groups of non-demented PD patients without further clarifying the cognitive status of the subjects. Any group of non-demented PD patients is likely to include patients with some degree of cognitive impairment. It is not known how many patients with cognitive impairment were included in previous studies or what level of impairment these patients had at the time of testing. The current study investigated the possibility that some

aspects of abnormal eye movement control found in PD are associated with a degree of cognitive impairment of the participants.

The following section summarises eye movement paradigms commonly used to investigate oculomotor control. Subsequent sections describe brain systems involved in the generation and execution of eye movements and the results of key studies of eye movement control in PD. An overview of the evidence of cognitive impairment in PD is then provided. The final section in the first chapter provides a summary of issues involved and rationale for the current study.

1.2 The study of eye movement control

When scanning the environment the eyes are moving constantly to realign the fovea with new objects of visual attention. These fast eye movements (or saccades) are overt motor responses that can be easily manipulated and accurately measured in a laboratory setting. Different tasks can be used to assess oculomotor control in terms of response latency, velocity, amplitude, spatial accuracy and error rates.

1.2.1 Reflexive and intentional (voluntary) saccades

In eye movement research a distinction is made between *reflexive* and *intentional* saccades. *Reflexive* saccades are eye movements triggered exogenously by the unpredictable onset of a visual stimulus. Moving or salient visual input can automatically attract attention and trigger a foveating saccade. An effort of will is required to suppress a reflexive saccade (Deubel, 1995). The direction and amplitude of reflexive saccades are determined by the location of the target. In contrast, *intentional* (also described as voluntary or volitional) saccades are triggered endogenously in compliance with a specific goal or task. The direction, amplitude, and timing of an *intentional* saccade can be contingent on, but are not fully determined by, the onset and location of a visual target. Normally a combination of endogenous and exogenous influences contributes to the programming of saccades. In an experimental setting, however, it is possible to investigate reflexive and intentional components of saccade generation separately.

Latencies of reflexive and intentional saccades can be modulated independently by manipulation of endogenous and exogenous influences on saccade production (Massen, 2004). This suggests that, at least in part, different neural pathways are involved in the generation of reflexive and of intentional saccades. The notion of different neural pathways for reflexive and intentional components of saccade production is also supported by findings that some pathological conditions can affect one type of saccade

and leave the other intact (T. Crawford et al., 1989; Crevits et al., 2004; Munoz & Everling, 2004). Additional evidence for the existence of two separate neural pathways is found in the bimodal distribution of latencies of saccadic responses in specific conditions of eye movement tasks (Fischer et al., 1993). The two neural pathways, reflecting exogenous and endogenous components of saccade programming, are thought to operate in parallel (Massen, 2004) until they converge in the neural structure where saccades will be triggered. The streams can be in competition with each other, and eye movements will be triggered by the winner of the 'race' (Fischer et al., 2000) or the result of 'competitive integration' (Van der Stigchel & Theeuwes, 2005) . Experimental eye movement paradigms are designed specifically to assess the cooperation and competition between reflexive and intentional influences on saccade generation.

1.2.2 Eye movement paradigms

Two areas of interest in eye movement research are reaction times (usually termed latencies) and the intentional inhibition of reflexive saccades. These two issues are thought to be related as it has been shown that the ability to inhibit unwanted reflexive saccades is affected by the latency at which they are triggered (Fischer et al., 2000; Massen, 2004). Manipulation of the presentation of fixation and target stimuli and specific task instructions in different eye movement paradigms are used to assess response latencies and voluntary saccadic control. Two common paradigms used in eye movement research, prosaccade and antisaccade tasks, will be discussed in the following section.

Prosaccade and antisaccade tasks

In the literature the terms prosaccade and reflexive saccade are sometimes used interchangeably. Here the term *prosaccade task* will be used to distinguish eye movement tasks where the response is to be made towards the location of a visual stimulus, from *antisaccade tasks* where the response is to be made away from the location of a visual stimulus. The direction of reflexive saccades is determined by the location of a visual stimulus, so all reflexive saccades are by definition prosaccades. However, not all prosaccades are reflexive saccades. Prosaccades may be reflexively triggered, but they can also be intentionally generated.

In a *prosaccade task* the subject is asked to fixate a central fixation point and to make a saccade towards the location of a peripherally appearing visual target. If the cue for the initiation of the saccade is the unexpected onset of the visual stimulus at an unpredictable location the task will promote the production of reflexively triggered

saccades. As the two neural pathways involved in saccade production operate in parallel this task will elicit not only exogenously triggered reflexive saccades, but also a number of saccades generated through the intentional system. Although different neural pathways may be involved in the production of reflexive and intentional saccades, overtly the two types of responses can only be distinguished by their latency. Reflexively triggered saccades will generally occur at shorter latencies than intentionally generated saccades. If the response in a prosaccade task is not to be triggered by the onset of the visual target, the task promotes the generation of intentional prosaccades. An example of an intentional prosaccade task is a delayed prosaccade task, where the saccadic response is to be withheld until a cue occurs some time after target onset. In this task the reflexive response has to be intentionally inhibited.

Reflexive saccades

In tasks promoting the production of reflexive saccades the subject is asked to fixate a central fixation stimulus and to look at a visual stimulus as quickly and accurately as possible, as soon as it appears. The timing and location of the peripheral stimulus are unpredictable. In this condition the reflexive and intentional system for saccade production operate in parallel towards the same goal.

Different task conditions can be created by manipulating the onset and offset of visual stimuli. These manipulations affect the average latency of responses elicited by the task. The shortest latencies are obtained in a *gap* condition. This condition is created by presenting a blank screen between fixation point offset and target onset. In the gap condition fixation is released exogenously before target onset. In the *immediate* condition, fixation point offset and target onset occur at the same time. In an *overlap* condition, meanwhile, the central fixation point remains visible for the duration of the trial. In both the immediate and the overlap condition the subject is fixating the central fixation point at the time of stimulus onset. However, fixation will not be released exogenously in the overlap condition as the fixation point remains visible during the trial. Average response latencies are shorter in the immediate condition than in the overlap condition, because exogenous release of fixation (by fixation point offset) facilitates the initiation of the response. This effect is thought to be associated with the automatic increase in the activity of saccade neurons when the activity of fixation neurons is decreased by fixation point offset.

The same mechanism is thought to be responsible for the shorter latencies in the gap condition compared to the immediate condition. This shortening of response times is

called the *gap effect* (e.g., Craig et al., 1999). The optimum duration of the gap has been found to be 200 ms, producing gap effects of up to 50 ms (Chan et al., 2005; Crevits & Vandierendonck, 2005).

Express saccades

Response latencies of healthy subjects on prosaccade trials with a gap show a bimodal frequency distribution, with a peak around latencies of 110 ms and a second peak around 160 ms (Fischer et al., 1993). Eye movements occurring within 80 ms of target onset are generally regarded as anticipatory movements and are not included in the analysis of saccadic responses. It has been suggested that responses occurring between 80 – 140 ms after the unpredictable onset of a visual target should be classified as 'express saccades' (Chan et al., 2005; Fischer et al., 2000; Klein & Fischer, 2005). The production of saccades with latencies in this range depends on neural activity in the superior colliculus (SC), the absence of a fixation stimulus at the time of target onset and a subject's natural predisposition (Fischer et al., 1993, Klein, 2005 #318). Some individuals seem to be naturally inclined to make more saccades with latencies in the express range than others Express saccades, then, are reflexive saccades identified as a special category only by latency. That is, all express saccades are reflexive, but not all reflexive saccades are necessarily express saccades. Classifying and counting these responses as a separate category may provide information regarding the distribution of saccadic latencies which would not be revealed by a mean latency value.

Intentional prosaccade trials

Intentional prosaccade tasks are often used to assess spatial accuracy of eye movements. One of these tasks is the memory-guided saccade task. In this task the target stimulus disappears before a saccade is initiated and the target location has to be remembered across a delay period. Predictive saccades are a special type of memory guided saccades. In these trials the subject memorises the target location, perhaps unintentionally, because a target is presented repeatedly at the same location.

Intentional prosaccade trials can also be used to assess a subject's ability to inhibit a reflexive response towards the target. In *delayed* prosaccade trials the participant is instructed to withhold the prosaccade until a cue occurs. Fixation point and target stimulus are both present during the delay and the fixation point offset or a tone can be the cue for saccade initiation. Delays between target onset and the cue for saccade initiation are usually in the range of 200 – 1400 ms in this task (Amador et al., 2005; Chan et al., 2005). In delayed prosaccade tasks the response can be planned as the

location of the target is visible, but should not be executed before the occurrence of the cue. A reflexive response triggered by the appearance of the visual stimulus is to be inhibited.

It is important to distinguish the *delayed* prosaccade task from the *overlap* condition of the reflexive task. The stimulus presentation in *overlap* and *delayed* prosaccade trials can be identical, but the instructions to the subject are different in the two tasks. In the overlap task the subject is told to make a saccade towards the target as quickly as possible after its appearance. In contrast, in the *delayed* task the subject is instructed to withhold a prosaccade after target onset until a further cue occurs. Efficient control of attentional resources and stable maintenance of fixation should prevent eye movements during the delay. A saccade before the occurrence of the cue is counted as a premature response or timing error.

Antisaccade trials

Another paradigm used to assess the generation of intentional saccades is the antisaccade task. On antisaccade trials visual stimuli appear generally at an unpredictable time and location. The subject is instructed not to look at the stimulus, but to make a saccade in the opposite direction instead, to a mirror position of the peripherally appearing visual stimulus. In a typical antisaccade trial the subject fixates a point at the centre of the display. Visual stimuli can appear peripherally either to the left or the right of the centre. If a stimulus appears for example at 10 deg to the right, the correct response on this task is a saccade to a location 10 deg to the left of the centre.

The antisaccade task assesses the ability to suppress a reflexive saccade towards the stimulus and the ability to generate a voluntary antisaccade (Hallett, 1978). As the timing and amplitude of the correct antisaccade is informed by the appearance and location of the visual stimulus, a covert shift of attention towards the visual stimulus is required before a correct antisaccade can be generated. Efficient control over visual attention (with or without the help of a visible fixation point) should prevent the unwanted reflexive saccade and allow the antisaccade to be programmed and initiated (Everling & Fischer, 1998). It is not known exactly how the amplitude and direction of the correct antisaccade are specified, but a transformation or manipulation of spatial information in working memory is required. Saccades in the direction of the visual stimulus are counted as directional errors.

Healthy adult subjects will make directional errors on 10 to 30% of antisaccade trials (Amador et al., 2005; Chan et al., 2005; Everling & Fischer, 1998). An abnormally high

proportion of errors can be attributed to either an impairment of the fixation system (e.g., too weak or slow) or impaired intentional saccade generation or both. The first impairment will be associated with more directional errors at short latencies, while the second impairment will be associated with correct antisaccades at long latencies (Fischer et al., 2000). The notion of the independence of these two processes is supported by evidence that the ability to use intentional fixation to inhibit unwanted saccades develops by the age of 10, while the ability to generate correct antisaccades does not mature until adulthood (Munoz et al., 1998). The question whether intentional fixation and intentional saccade generation can be affected differentially in pathological conditions still needs clarification (Everling & Fischer, 1998).

Modulation of latencies in the antisaccade task

Similar to prosaccade latencies, response latencies in the antisaccade task can be modulated by the temporal arrangement of the presentation of fixation and target stimuli. The insertion of a temporal gap of 200 ms between fixation point offset and target onset in the antisaccade task shortens the average latency of directional errors compared to the immediate antisaccade condition (Chan et al., 2005) (Crevits & Vandierendonck, 2005).

The insertion of a temporal gap also shortens average latencies of correct antisaccades (Crevits & Vandierendonck, 2005). A significant gap effect on correct antisaccade trials indicates that the automatic increase in the activity of saccade related neurons after the exogenous release of fixation not only benefits the generation of visually triggered reflexive saccades, but also the generation of intentional saccades.

Control of reflexive and intentional saccades

It has been suggested that the mechanisms involved in the inhibition of reflexive and intentional saccades may depend on, at least partly, independent neural pathways. Dissociation has been found in the effect of pathological conditions on the two types of inhibition. Patients with fronto-temporal dementia were impaired in the inhibition of reflexive as well as intentional responses on a delayed antisaccade task. Patients with supranuclear palsy, however, showed only an impairment of reflexive saccade inhibition, while patients with Gilles de Tourette syndrome were only impaired at intentional saccade inhibition (Meyniel et al., 2005).

An antisaccade task with a delay condition can be used to address these specific issues. In this task the subject is instructed to try and prevent a saccade towards the visual

stimulus *and* delay the initiation of the antisaccade until a cue occurs (e.g., fixation stimulus offset or a tone). As discussed above for the delayed prosaccade task, in the delayed antisaccade task the response can be planned, but should not be executed before the cue occurs. In this task premature prosaccades are counted as 'directional and timing' errors, premature antisaccades are counted as timing errors and prosaccades after fixation point offset are counted as directional errors. In this task the proportion of 'directional and timing' errors is a measure of the ability to inhibit a reflexive response. The proportion of timing errors is a measure of the ability to inhibit a predictable intentional saccade.

Different modes of control in eye movement tasks

Prosaccade tasks with a delay and antisaccade tasks with or without delay assess the ability to control reflexive saccades in favour of intentional eye movements. The key difference between the tasks is that in the delayed prosaccade task the incorrect reflexive response and the correct intentional response are overtly the same eye movement. In this task stable fixation is required to prevent a response during the delay. The cognitive process involved in continued fixation is different from the cognitive processing required in the antisaccade task. In the antisaccade tasks the reflexive response competes with an intentional response involving additional cognitive processing.

1.2.3 Eye movement tasks used in the current study

The current study used prosaccade and antisaccade tasks to investigate reflexive and intentional aspects of oculomotor control in PD patients. To enable assessment and comparisons of different types and levels of control each task was presented in a gap, immediate and delayed condition. The next section will examine the neural pathways contributing to reflexive and intentional components of saccade generation.

1.3 Brain systems involved in saccade generation

As discussed earlier, a distinction is made in eye movement research between reflexive and intentional (voluntary) aspects of saccadic behaviour. Reflexive, exogenously triggered, orienting responses are a basic function of brain. With the evolution of complex brains, functions have developed which inhibit automatic orienting responses, and allow the production of intentional eye movements instead. Intentional response control operates through inhibitory neural projections to areas of the brain where responses are triggered.

A large number of brain systems cooperate in the production of eye movements. Spatial information for saccades comes from various cortical areas, including dorsolateral prefrontal cortex (DLPFC), frontal eye fields (FEF), supplementary eye fields (SEF), parietal areas (superior and inferior lobules) and visual areas V1 and V5. Frontal and parietal areas are connected to each other and to the cerebellum and the superior colliculus (SC) via direct and indirect projections. The indirect route to the SC includes the basal ganglia (BG). Basal ganglia circuits integrate and prioritise various cortical signals and project the result of this modulation to areas involved in response generation and back to cortical areas. This process contributes to the modulation of saccade related neural activity in the SC. Timing of the start and end of eye movements is determined in the dorsal vermis and fastigial nucleus of the cerebellum. By controlling bursts of contralateral and ipsilateral neural activity these nuclei determine the accuracy of saccades. Fixations and saccades are finally executed by neural activity in pontine nuclei in the brainstem (Leigh & Kennard, 2004).

Brainstem

In the pontine nuclei of the brainstem reticular formation two mutually inhibitory neuronal populations determine the start and end of eye movements through alternating periods of movement with periods of fixation. So called ‘burst’ neurons are active during saccades, and silent during fixation, while ‘omnipause’ neurons are active during fixation and suppressed during saccades. These brainstem cells receive their main information specifying timing and spatial coordinates of saccades from the cerebellar vermis and the SC respectively (Leigh & Kennard, 2004).

Superior colliculus

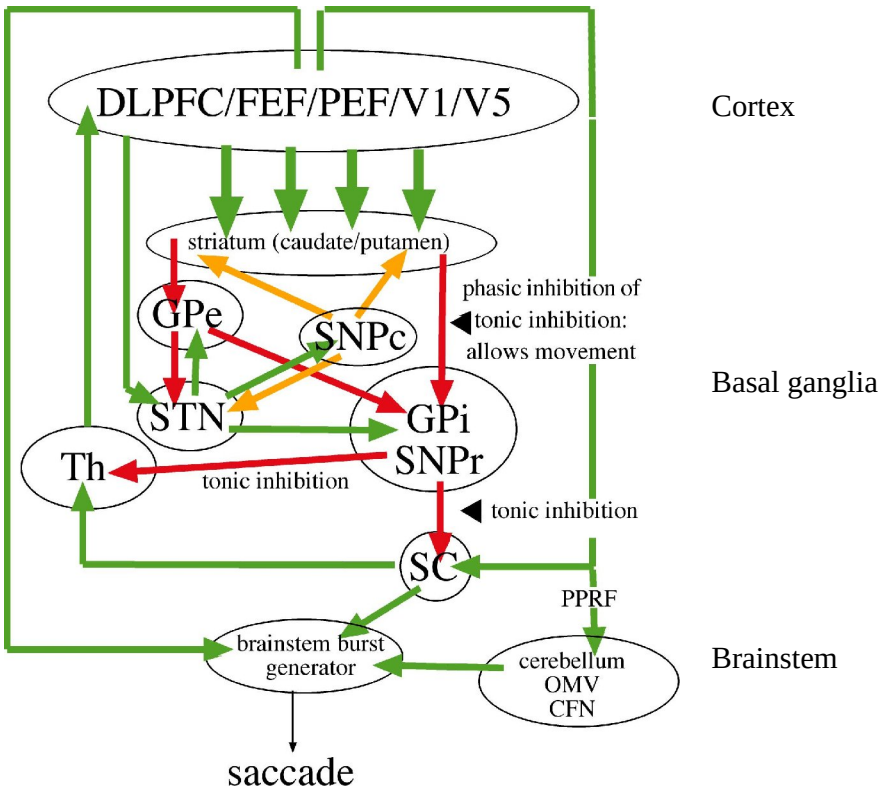
Bursts of saccade related activity in the cerebellum are temporally related to eye movements. In contrast, neurons in the SC are activated retinotopically i.e., each part of

the visual field is connected to a different set of neurons (Leigh & Kennard, 2004). The centre of the visual field is represented at the rostral pole of the SC, which is active during fixation and projects to omnipause neurons. The peripheral field is represented in the caudal parts of the SC, which project to saccadic burst neurons. When neurons at the rostral pole of the SC stop firing and more caudally located SC neurons become active a saccade is initiated. Small saccades are produced by neural activity close to the rostral pole, while saccades of larger amplitudes are associated with activity nearer the caudal pole. The exact mechanism involved in specifying the amplitude of a saccade is not yet clear, but it seems that the temporal and spatial coordinates of each saccade depend on the mutually inhibitory activity of rostral and caudal SC neurons (Everling & Fischer, 1998) (Leigh & Kennard, 2004). The arrangement of neurons in the SC can be described as an overall 'motor map' mapping the visual field in terms of saccadic amplitudes (Massen, 2004).

Projections to the superior colliculus

Two particularly important inputs to the SC are the direct excitatory input from frontal, parietal and visual cortical areas and the GABAergic inhibitory projection from the substantia nigra pars reticulata (SNPr). The inhibitory output from the BG via the SNPr represents the influence from cortical areas via an indirect route (see 0). The direct and indirect pathways expressing cortical influences in the SC have different functions in saccade execution. The first provides signals that potentially trigger saccades. The latter exerts a control function, through global inhibition of neural structures where unwanted saccades would be triggered (if left uninhibited) combined with specific disinhibition of neuronal activity required for the execution of desired eye movements or fixation (Hikosaka et al., 2000).

The combined or integrated result of signals from different cortical areas determines the production or suppression of erroneous saccades in delayed saccade or antisaccade tasks. Lesion and monkey studies and neuro-imaging techniques have been used to try and clarify the individual contributions of FEF, SEF, and DLPFC to inhibitory and excitatory components of intentional saccade production (Pierrot-Deseilligny et al., 2003; Schall, 2002). However, the interactions between and specific roles of these neural structures in oculomotor control still need clarification (Leigh & Kennard, 2004).



Neural influences on saccade generation. Green lines represent excitatory connections, red lines represent GABA-ergic inhibitory connections and orange lines show dopaminergic connections. DLPFC = dorsolateral prefrontal cortex, FEF = frontal eye fields, PEF = parietal eye field, V1 = visual area, GPe = globus pallidus external segment, GPi = globus pallidus internal segment, SNPr = substantia nigra pars reticulata, SNPc = substantia nigra pars compacta, Th = thalamus, STN = subthalamic nucleus, SC = superior colliculus.

Basal ganglia and superior colliculus

The drive to make a saccade of a particular size is determined by neurons arranged in spatial maps in cortical areas including DLPFC, frontal eye fields (FEF), supplementary eye fields (SEF), parietal eye fields (PEF) and visual areas V1 and V5. Influence from the BG will inhibit or disinhibit neural structures where saccades are triggered. This BG function is implemented via a tonic (i.e., not modulated by sensory information) inhibitory output from SNPr on the SC, which can be selectively interrupted when a saccade is to be initiated. The role of the inhibition of the SC is to prevent excitatory signals from triggering unwanted saccades. This tonic inhibition has to be interrupted not only before saccade neurons can burst and generate a saccade, but also during periods of fixation to allow the omnipause neurons to be activated and burst neurons to be inhibited. This means that before a saccade is generated an area of the SC, projecting to a specific population of burst neurons on the brain stem, is to be released from the tonic inhibitory influence of the BG output. During fixation another population of SC neurons, projecting to the omnipause neurons in the brain stem, is released from the tonic inhibitory influence. A GABA-ergic projection from the caudate nucleus, one of

the structures in the striatum, supplies a phasic inhibitory signal, lifting the tonic inhibitory influence in the appropriate area of the SC. During intentional fixation the rostral pole of the SC must be disinhibited, and for a saccade to occur a more caudal location of the SC must be disinhibited (Hikosaka et al., 2000).

Fixation and the superior colliculus

During fixation the rostral pole of the SC activates omnipause neurons in the brainstem. Mutually inhibitory connections ensure that while omnipause neurons are active, burst neurons are inhibited. This mechanism is involved not only in the inhibition of unwanted saccades but also in the delay of predictable or planned eye movements (Leigh & Kennard, 2004). The inhibitory influence of fixation can prevent the burst neurons from reaching the level of activity that would trigger a saccade. Impairment of this function can presumably be associated with a higher than normal baseline level of activity or with a lowering of the threshold level of neural activity needed to trigger a saccade.

Fixation related activity in the SC is relevant to the latency of saccades. As discussed earlier in the section on the gap condition of eye movement tasks, the release of fixation, triggered exogenously by the offset of the fixation stimulus, results in shorter response latencies. The decrease in the activity of the omnipause neurons automatically increases activity of burst neurons. This interaction prepares the oculomotor system for the rapid production of a saccade (Leigh & Kennard, 2004; Munoz & Fecteau, 2002).

The role of dopamine in BG functioning

DA projections from SNPc modulate inhibitory and disinhibitory BG outputs via two different pathways each consisting of mainly D1 or D2 receptors. D1 and D2 receptors respond preferentially to information that has been linked to a rewarding experience in the past or is expected to provide a positive experience in the future (Schultz, 1998). D1 receptors have an excitatory and D2 receptors have an inhibitory influence on neural activity. Efficient selective activation of an appropriate (oculomotor) response in competition with irrelevant distractors depends crucially on the presence of DA-ergic innervation in the striatum (Hikosaka et al., 2000). DA transmission is involved in the selective enhancement of a saccade related signal from the caudate, resulting in faster GABA-ergic suppression of SNPr neurons. This suppression would in turn cause a faster disinhibition and allow a stronger burst of saccade related neurons in the SC. This mechanism may determine the time needed to reach the neural firing rate required to trigger a saccade (Hikosaka et al., 2000; Schall & Hanes, 1998).

In summary, oculomotor behaviour consists of alternating eye movements with periods of fixation. The alternation between movement and fixation is implemented by mutually inhibitory activations of burst neurons and omnipause neurons in the lower brain stem. The activity of these two neural populations in the brainstem is associated with neural signals encoding spatial aspects of saccade production in the SC. Excitatory signals for reflexive saccades are provided by parietal eye fields, for intentional saccades by frontal eye fields. The contribution of each of these neural structures to the correct performance of the antisacade task is still to be defined. Different parts of the SC are active during fixation and during eye movements. For fixation and for eye movements to occur a phasic striatal signal is required to release the appropriate part of the SC from the tonic inhibitory influence of the SNPr. DA transmission is involved in the efficiency of the selective disinhibitory signal from the striatum as well as the tonic inhibitory influence from SNPr on the SC.

1.4 Eye movement control in Parkinson's disease

Evidence of abnormal oculomotor behaviour has been found in many groups of PD patients. This section explores the results of investigations using single horizontal saccade tasks (see also Table 1). Single horizontal saccade tasks elicit one eye movement response per trial and each response is analysed individually. Some questions remain after several comprehensive investigations. The merits of suggested explanations are discussed.

1.4.1 Overview of previous studies

Results of previous studies are not always easy to compare due to differences in methodology or sample characteristics. Nonetheless, a general picture has emerged of normal or faster than normal responding on tasks eliciting reflexive saccades and slower, less accurate responses and increased error rates on intentional saccade tasks in PD.

Reflexive saccades

Some studies have reported normal latencies of reflexive saccades in non-demented PD patients (Briand et al., 1999; T. Crawford et al., 1989; Crevits et al., 2004; Mosimann et al., 2005; Shaunak et al., 1999; Vidailhet et al., 1994; Yoshida et al., 2002). Other investigations have found faster than normal responses and increased production of express saccades in non-demented PD patients (Amador et al., 2005; Armstrong et al., 2002; Briand et al., 2001; Chan et al., 2005). Slower than normal reflexive saccades were reported only in a group of demented PD patients (Mosimann et al., 2005).

Intentional saccades

Memory-guided saccade trials have consistently shown abnormally low gain (or hypometria) of primary saccades in PD patients (T. J. Crawford et al., 1989; Lueck et al., 1992; Nakamura et al., 1994; Shaunak et al., 1999; Yoshida et al., 2002). The gain of the primary saccade refers to the proportion of the intended total amplitude of the saccade reached after the first movement of the eye. If the gain of the primary saccade is low several subsequent saccades may be required to reach the desired final eye position.

Antisaccades

Several investigations have suggested that error rate, gain, latency and velocity of antisaccade performance in mild to moderate cases of PD are normal (Kitagawa et al., 1994; Lueck et al., 1990; Mosimann et al., 2005; Vidailhet et al., 1994). Increased latencies and higher error rates in the antisaccade task were reported in moderate to

advanced cases of PD patients (Kitagawa et al., 1994) (Crevits & De Ridder, 1997; Crevits et al., 2000), and in PD-D (Mosimann et al., 2005). One study found a dissociation of increased error rates and longer latencies in the antisaccade task. Error rates were associated with the use of anticholinergics, while slowed initiation of antisaccades in advanced patients was associated with frontal lobe dysfunction (Kitagawa et al., 1994). Another study, using an antisaccade task with a gap, found that mild to moderately affected PD patients made more errors *and* had longer latencies of correct antisaccades than healthy control participants (Briand et al., 1999).

1.4.2 Recent studies

Three studies recently further investigated and clarified specific aspects of intentional eye movement control in non-demented PD patients:

- Crevits, Vandierendonck, Stuyven, Verschaete and Wildenbeest (2004) used a prosaccade task, cued by a centrally located arrow, to address the question whether the intentional saccade deficit reported in some studies of PD patients was associated with specific aspects of the antisaccade task. It had been suggested that longer latencies of antisaccades in PD may have been associated with the absence of a visual target. However, this study found that even when a visual target was present and there was no need to inhibit a reflexive saccade, intentional saccades were made at significantly longer latencies by mild to moderate non-demented PD patients compared to healthy control subjects. The authors conclude that the results confirm the presence of an intentional response deficit in PD (Crevits et al., 2004).
- Amador, Hood, Schiess, Izor and Sereno (2005) investigated cognitive components of saccade production in a group of non-demented PD patients. Suppression of reflexive saccades and intentional saccade execution were assessed with antisaccade tasks, in an overlap and a delay condition. Latencies of correct antisaccades as well as the proportion of errors were found to be increased in the PD group compared to the healthy control group. Both groups made fewer directional errors in the delay condition, but PD patients were still impaired relative to the control group. The authors interpreted the results as evidence that a deficit of the intentional system caused both impaired generation of intentional saccades and the increased proportion of reflexive errors in PD (Amador et al., 2005).
- Chan, Armstrong, Pari, Riopelle and Munoz (2005) used a comprehensive range of tasks to investigate the relationships between reflexive saccade latencies, response inhibition, and intentional saccade generation in non-demented PD patients. Pro-

and antisaccade tasks were presented in three different conditions (gap, overlap, and delayed). This study reported that in prosaccade trials the mean latency was normal, but the proportion of express saccade was larger in the PD group than in the control group. This difference was significant specifically in the overlap condition, where control subjects made very few express saccades. The PD patients also made more directional errors and were slow to generate correct antisaccades. Increased error rates (timing as well as directional errors) were also found in both the delayed prosaccade and delayed antisaccade trials. The authors conclude that the results are consistent with a general deficit of automatic response inhibition in PD, resulting from impairment of frontal-basal-ganglia circuits (Chan et al., 2005).

In summary, the evidence for abnormal eye movement control in non-demented PD patients is not entirely clear. Reflexive saccade production is found to be normal in some groups of non-demented PD patients and faster than normal in others. Deficits of intentional saccade production are consistently found when delayed and memory-guided saccade tasks are used. In contrast, antisaccade trials have shown normal performance in some groups of non-demented PD patients, but impaired performance in others. Table 1 shows an overview of eye movement studies in PD and a short description of their findings.

Table 1 Overview of eye movement studies in Parkinson's disease, comparing patient groups and healthy age matched control subjects

Author	Reflexive Saccades	Intentional Saccades
Amador et al. 2005	-	Non-demented PDs were slower to respond and made more reflexive errors in antisaccade and delayed antisaccade tasks than controls
Mosimann et al. 2005	Non-demented PDs respond normally, but PD-Ds respond slower than controls	Non-demented PDs responses are normal, PD-Ds were slower to respond and made more errors in anti, decision and predictive saccade tasks than controls
Chan et al. 2005	Non-demented PDs make more express saccades than controls	Non-demented PDs were slower to respond and made more errors in antisaccade and delayed saccade tasks than controls
Crevits et al. 2004	Non-demented PDs respond normally	Non-demented PDs were slower to respond and made more errors in intentional saccade task than controls
Kingstone et al. 2002	Mild to moderate PDs respond faster than controls	Mild to moderate PDs are unimpaired in antisaccade task
Armstrong et al. 2002	Non-demented PDs respond faster and make more express saccades than controls	Non-demented PDs were slower to respond and made more errors in antisaccade and delayed saccade tasks than controls
Briand et al. 2001	PDs respond faster than controls on reflexive visual orienting task	-
Crevits et al. 2000	-	Advanced PD patients made more errors on antisaccade task than controls
Briand et al. 1999	PDs respond normally	Non-demented PDs were slower to respond and made more errors on antisaccade task
Shaunak et al. 1999	PDs respond normally	PDs memory-guided saccades are hypometric compared to controls
Nakamura et al. 1997	-	PDs memory-guided saccades are hypometric compared to controls
Crevits et al. 1997	-	Advanced PDs made more errors on antisaccade task
Kitagawa et al. 1994	-	Mild PDs unimpaired, but advanced PDs were slower to respond and made more errors on antisaccade task
Vidailhet et al. 1994	-	Mild PDs unimpaired on antisaccade task
Lueck et al. 1990	-	Mild PDs unimpaired in latency and gain on antisaccade task, but memory-guided saccades are hypometric
Crawford et al. 1989	PDs respond normally	PDs memory-guided saccades are hypometric

1.4.3 Potential explanations for contradictory results

Auditory cues

Briandet al. found both normal (Briand et al., 1999) and faster reflexive response latencies in PD (Briand et al., 2001) with a gap paradigm. The different outcomes may have been due to the use of a tone as a cue for saccade initiation which coincided with target onset after the gap in the first study. The additional cue of a tone sounding when a saccade should be generated may have reduced the gap effect in PD patients more than in healthy control subjects. As discussed earlier, the offset of a fixation stimulus is thought to automatically release the inhibition on saccade related neurons in preparation for an upcoming saccade. The mechanism of this effect is twofold: fixation point offset serves as a warning signal that a target is coming up and it results in exogenous decrease of the fixation neurons' activity. A tone by itself, before target onset, can have a warning effect also (Kingstone & Klein, 1993). The effect of fixation point offset may be attenuated when a tone is used as a cue for response initiation after the gap, temporally coinciding with target onset.

Reflexive saccade latencies and error rates

A tendency to produce very fast reflexive responses may affect the proportion of errors produced in delayed saccade and antisaccade tasks (Biscaldi et al., 1996; Massen, 2004; Munoz & Everling, 2004). Studies have shown that some PD patients may initiate reflexive responses faster than healthy controls (Briand et al., 2001; Kingstone et al., 2002). This tendency can be reflected in an increased rate of express saccade production rather than in the mean response latency (Chan et al., 2005) (See Table 2). The groups of PD patients in the studies that did not find an increased proportion of errors in antisaccade tasks may have contained fewer subjects with the tendency to make very fast reflexive saccades. Alternatively, task conditions may not have been promoting extra fast reflexive responses. It is not clear if the tendency to make an abnormally high percentage of express saccades is related to PD, its treatment or to other personal characteristics.

Table 2 Studies that found faster than normal reflexive saccades and/or more express saccades in PD. The proportion of express saccades is shown as a percentage of trials. Latencies are shown in ms. * indicates that the difference between the groups was significant, p<.05.

Author	Prosaccade task with a gap		Prosaccade task with an overlap	
	PD	Controls	PD	Controls
Chan et al. (2005)	19% express	3% express	5% express*	1% express
	267 ms latency	276 ms latency	312 ms latency	320 ms latency
Kingstone et al. (2002)	213 ms latency*	273 ms latency	287 ms latency*	372 ms latency
Briand et al. (2001)	-	-	315 ms latency*	373 ms latency

Executive control

Chan et al. (2005) attribute the higher error and express saccade rates of their PD group to a general loss of inhibitory control over automatic responses. This implies a loss of executive control in the PD group, as 'executive control' is the putative brain function that allows efficient voluntary control over automatic or habitual responding (Heyder et al., 2004). The delayed prosaccade and antisaccade tasks can be regarded as tests of executive control (Reuter & Kathmann, 2004). It has been suggested that *if* there is a loss of cognitive abilities in PD it is associated with a gradual loss of executive functions (Bosboom et al., 2004; C. Janvin et al., 2003; Woods, 2003). It is likely then that groups of non-demented PD patients contain a number of subjects suffering some degree of executive dysfunction. So far, cognitive function of the PD patients involved in eye movement studies has not been assessed beyond the distinction between demented and non-demented patients. Results of studies using delayed or antisaccade tasks may therefore depend on varying degrees of executive dysfunction of the participants. Neuropsychological testing can help to assess the nature and severity of deficits of cognitive function or executive control in the patient group and clarify this issue.

Prefrontal cortical functions

It has been suggested that impaired performance on antisaccade tasks in PD indicates a spread of pathology to prefrontal cortical functions (Blekher et al., 2000). If this is the case it may be that samples of people with PD showing impaired antisaccade performance included a larger percentage of patients with frontal lobe impairment. Inhibition of reflexive responses has traditionally been equated with prefrontal cortical function, because patients with frontal pathology show deficits on tests designed to

challenge the suppression of automatic responses. Impaired performance on antisaccade tests may indeed be associated with altered frontal lobe functioning. Increased response latencies and error rates in antisaccade trials have been found in schizophrenia (Crawford et al., 2002; Hutton et al., 2004; Nieman et al., 2000; Reuter & Kathmann, 2004), Alzheimer's disease (Crawford et al., 2005), and in patients with frontal lesions (Guitton et al., 1985; Roberts, 1994). However, the nature and origin of the impaired performance on the antisaccade task in these patient populations is not clear yet (Everling & Fischer, 1998). Many cortical and subcortical areas are involved in the generation of intentional saccades and in the control of intentional fixation. Disruption in any of those may result in impaired saccade initiation or impaired fixation and increased error rates on the antisaccade task. It has, for instance, also been suggested that GABA-ergic dysfunction of the basal ganglia may play a direct role in impaired suppression of reflexive saccades (Cassady et al., 1993). It may therefore not be safe to interpret a deficit on the antisaccade task as evidence for (pre)frontal pathology (Everling & Fischer, 1998). This issue is difficult to address without brain-imaging techniques to assess cortical atrophy or changes in neurotransmitter systems or brain metabolism.

In summary, abnormal performance on delayed prosaccade, antisaccade, and reflexive eye movement tasks may be attributable to different underlying mechanisms. In some PD patients the impaired performance may be associated with a degree of cognitive impairment or executive dysfunction. In others abnormal saccadic response patterns may be associated with a tendency to make very fast reflexive saccades. The mechanisms of executive function and express saccade production may also be associated with each other. The current study aims to clarify these issues with careful neuropsychological testing in combination with detailed analysis of saccadic response latencies and error rates on a variety of eye movement tasks.

1.5 Cognition in Parkinson's disease

PD is generally considered to be a disorder of motor control. However, the evidence that PD, in addition to motor impairments, will cause cognitive deficits in some patients has been well documented over recent years (Bosboom et al., 2004; C. Janvin et al., 2003; Woods, 2003). Differences in motor as well as cognitive symptoms contribute to the heterogeneity of PD (Lewis et al., 2005). How the disease will affect cognitive and motor functions of a particular patient depends on interactions between pathology and personal characteristics.

PD affects specific types of neurons which are susceptible to the disease. The spread of neuropathology starts in the dorsal nucleus of the vagal nerve in the medulla and progresses upwards until it finally reaches the cerebral cortex (Braak et al., 2004). The first stages of the disease are not accompanied by overt symptoms. Motor symptoms become only apparent when the disease process has reached midbrain structures, including striatum and substantia nigra. These midbrain structures are also involved in efficient cognitive functioning, providing crucial connections between distributed cortical areas (Hayes et al., 1998).

Some PD patients will suffer a detectable loss of cognitive skills and functions. A proportion of these patients will decline into a state of frank dementia. For these patients ordering their thoughts even for the performance of daily routines becomes problematic and they may lose the ability to live life independently. Age at PD onset, severity of motor symptoms, duration of the disease, side effects of long-term use of medication and a low prodromal level of cognitive functioning are often cited as risk factors for serious cognitive decline in PD (Bosboom et al., 2004).

Reports of frequency, nature and severity of cognitive impairment in PD vary according to methods used to select patients, assess cognition, and define deficits. In an investigation of neuropsychological profiles in PD a mild cognitive impairment was found in 55% of non-demented PD patients (C. Janvin et al., 2003). The estimate of the proportion of PD patients whose cognitive decline will eventually result in dementia varies from 20 - 80% depending on criteria used (McKeith, 2004; Woods, 2003).

1.5.1 Overview of cognition in PD

In an attempt to distinguish the specific nature of mental decline associated with PD from other types of cognitive impairment, it has been suggested that it can be best described as a gradual loss of executive function (Bosboom et al., 2004). Executive function or executive control is a neuropsychological concept used to refer to a variety

of basic cognitive functions, including inhibition, shifting of attention, planning, task monitoring and management (Heyder et al., 2004). Intact executive function or executive control allows quick and appropriate responses to changing demands of the environment, by preventing automatic unwanted reactions and ignoring irrelevant information (Hazy et al., 2006). A degree of executive dysfunction means that some voluntary control over cognitive and motor functions has been lost. While the loss of motor control is obvious in PD, a decline in control over cognitive functions can go undetected for some time.

Sometimes in the literature the terms executive control and (pre)frontal brain functioning have been used as synonyms. More recently, however, the conflation of function and anatomy this implies has been questioned. Executive function is now thought of rather as the result of efficient cooperation and coordination of distributed neural populations (Hazy et al., 2006). The concept of executive control as an emergent function of anatomically distributed neural processes is relevant to PD. Communication and cooperation between association areas and frontal cortex depend crucially on efficient connections via midbrain structures (Braak et al., 2004). In contrast to localised cortical brain lesions which result in specific cognitive deficits, the spreading nature of pathology in PD is more likely to cause a gradually worsening impairment of basic brain functions.

Cognitive assessment

Standardised neuropsychological tests are used in the assessment of specific cognitive functions. Tests of memory, working memory, visuospatial and verbal skills can be considered to assess abilities in separate cognitive domains. Sometimes executive function is also considered a cognitive domain. However, tests of executive function generally involve one or more of the other domains as well, and vice versa: most tests of a specific cognitive domain involve some use of executive functions for their performance.

1.5.2 Overview of neuropsychological profiles in PD

Many studies have investigated neuropsychological profiles of PD patients. Early reviews of cognitive function in PD indicated that deficits on the Wisconsin Card Sorting Test (WCST) and word fluency can be present from the early stages in PD (Gotham et al., 1988). Impaired performance on these tasks is generally considered evidence of a degree of executive dysfunction. It has often been observed since that cognitive deficits of PD patients can resemble the executive dysfunction of frontal

patients (Cools et al., 2001; Dubois & Pillon, 1997; Muller et al., 2000; A. M. Owen et al., 1992; Pillon et al., 1998; Robbins et al., 1994).

Analysis of the specific nature of deficits found in PD has clarified the presence of these 'frontal-like' deficits over recent years e.g.,(Cools et al., 2001; S. J. Lewis et al., 2003; S. J. G. Lewis et al., 2003; A. M. Owen & Doyon, 1999; Adrian M. Owen et al., 1997; Swainson et al., 2000). It had been suggested that working memory tasks involving spatial information may be more sensitive to deficits in PD than tasks involving verbal or object information (Adrian M. Owen et al., 1997) (Le Bras et al., 1999; Postle et al., 1997). However, when Lewis et al. (2003) explored the nature of cognitive heterogeneity in a group of mildly affected PD patients, it was found that if PD patients had a working memory deficit, the impairment was not domain specific. A subgroup of patients was identified on the basis of impaired performance on a variant of the Tower of London task. This test is a visuospatial test of executive function, involving manipulation of spatial information in working memory. This subgroup of patients also performed significantly worse on a task involving the manipulation of verbal information compared to the unimpaired PD group. The sensitivity of the test depended on the type of processing required, rather than the nature of the information to be manipulated. Neither group of PD patients had a deficit on tests involving the maintenance or retrieval of information in working memory. The authors concluded that manipulation of information in working memory can be affected, while maintenance and recall functions of working memory may be spared (A. M. Owen et al., 1992).

Longitudinal studies are another valuable source of information regarding the development of cognitive impairment in PD. Type and frequency of cognitive deficits have been recorded in large groups of initially non-demented PD patients (Jacobs et al., 1995; Janvin et al., 2003; Mahieux et al., 1998). One of these studies (Jacobs et al., 1995) retrospectively found that in their sample of initially non-demented PD patients' verbal fluency tests proved retrospectively most sensitive to incipient dementia. Letter fluency is a verbal test, asking the subject to generate words starting with a particular letter. The test also involves executive control, as it requires inhibition of the natural semantic associations of words in favour of the arbitrary letter requirement. The sensitivity of the letter fluency test for developing dementia in PD was confirmed by Mahieux et al. (1998). In addition Mahieux et al. identified the WAIS picture completion test and the Stroop test of executive control as sensitive to cognitive impairment in PD. Another longitudinal study assessed cognitive functions of non-demented PD patients in different domains, including executive control, visual memory

and visuospatial processing (Janvin et al., 2003). This study found that 55% of 76 non-demented PD patients scored 2 standard deviations, or more, below the mean of a control group on at least one of the tests. The impairment of some of these patients was limited to the Stroop test (assessing executive control), others were only impaired on the tests of visual recognition memory or visuospatial processing, while the rest had a deficit on all three tests. Follow-up testing after 4 years revealed that 33% of the initially non-demented patients had developed dementia. Retrospectively these investigators identified the Stroop test of executive function as the best predictor of later development of dementia (Janvin et al., 2005).

Woods and Troster (2003) investigated neuropsychological profiles of people with PD. A large number of non-demented patients were tested on a battery of neuropsychological tests. After one year the group was retested and 20 patients (17%) were identified who fitted the clinical criteria for a diagnosis of PD with dementia (PD-D). After taking into account demographic characteristics known to be risk factors for PD-D, the initial test scores of 18 newly diagnosed PD-D patients were compared to the scores of 18 PDs who were still non-demented at follow up. The PD-D group had significantly lower scores on digits backwards (WMS-R), acquisition and recognition of a list of words (CVLT), and had made more perseverative errors on the WCST compared to the PD group at the time of initial screening.

Neural substrate of cognitive impairment in PD

Cognitive impairment in the later stages of PD is likely to involve disruption of a variety of neural populations and neurotransmitter systems. As the variation in symptoms and disease progression in PD has been well documented (Foltynie et al., 2002) cognitive symptoms in PD may also have different underlying neural pathology. Janvin and Aarsland (2005) make a distinction between cortical and subcortical neuropsychological profiles of dementia. The distinction refers to the pattern of relatively spared and impaired cognitive functions. A cortical profile reflects the relatively more severe impairment on tests of memory function compared to the scores from tests of executive function. Their study revealed that of a group of 50 PD-D patients 28 patients fitted the criteria for a subcortical profile of dementia and 22 the criteria for a cortical profile of dementia. This is consistent with earlier reports of the same distinction in non-demented PD patients (Foltynie et al., 2002; C. Janvin et al., 2003). The authors acknowledge that the tests used, the Dementia Rating Scale (DRS), are not particularly sensitive to deficits in some specific cognitive functions (e.g., visuospatial abilities, shifting of attention, or

language). A more comprehensive battery of tests may have more potential to clarify the underlying nature and progression of different dementias at varying stages of mental decline.

1.5.3 Issues related to neuropsychological testing

Executive function, working memory and attention are closely related concepts. Working memory refers to the ability to maintain and manipulate information in the absence of immediate sensory input. Attention is a selective process that activates appropriate signals for representation in working memory. Executive function or executive control refers to the general ability to select, maintain, update and manipulate the content of working memory efficiently. For example, the ability to quickly change strategies to solve different problems is evidence of intact executive control.

Neuropsychological tests are designed to identify impairments in specific cognitive domains. The nature of the information involved in a neuropsychological test may belong to a specific domain (e.g., verbal or visuo-spatial). However, as discussed above the sensitivity of a particular test for the detection of a cognitive deficit in PD may depend on the type of processing required. Different interrelated cognitive processes can be identified. Maintenance of information is a basic function of working memory. Information is kept instantly available, or “on-line”. Retrieval of items of information in working memory depends on intact maintenance function. Manipulation of items in working memory depends on intact maintenance and retrieval functions.

1.6 Rationale for the present study

Previous studies suggest that aspects of intentional oculomotor control are affected in PD. It is also known that cognition can be impaired in PD. Working memory processes are involved in the performance of oculomotor tasks as well as in cognitive functioning. The current study was designed to investigate the possibility that some aspects of abnormal eye movement control are associated with cognitive impairments. Analysis of the key processes involved in each domain will clarify similarities and differences between processing requirements in eye movement and cognitive tasks.

1.6.1 Processes involved in eye movement control and neuropsychological tests

Two factors determine performance on eye movement tasks, reflecting exogenous and endogenous components of eye movement control:

- The spatial and temporal arrangement of fixation and target stimuli
- Task instructions, for example to delay, inhibit, or generate a specific response

Two main factors influence neuropsychological test performance:

- Nature of information involved in the task, for example verbal or visuospatial
- Type of processing required (e.g., maintenance, retrieval and/or manipulation)

The level and nature of cognitive processing required for the performance of eye movement tasks depends on specific task instructions. Reflexive tasks require little processing of information for their correct performance. In these tasks visual information (the stimulus) is allowed to trigger the response more or less automatically. When the task requires the subject to delay an automatic (reflexive) response a voluntary effort is required to maintain stable fixation during the delay period. When the task requires the subject to look away from the stimulus, as in the antisaccade task, a shift of attention and manipulation of information is required to specify spatial coordinates for the correct response.

Cognitive processes involved in the performance of neuropsychological tests are more complex than in the oculomotor tasks, but some key elements can be identified. Some tasks require selective visual attention only, and little cognitive processing. Memory tests require maintenance and encoding of information to allow retrieval after a delay. Manipulation of the information in working memory (e.g., reordering or categorising) can facilitate retrieval. Tests of executive function usually involve intentional control over automatic or habitual responses in favour of arbitrary task requirements. Working memory tasks involve maintenance, manipulation and retrieval of information after a

short delay. Tasks were selected to allow as clear an assessment as possible of component processes contributing to performance of both oculomotor and neuropsychological tasks.

1.6.2 Eye movement tasks

For the assessment of intentional eye movement control delayed and antisaccade tasks were chosen. Reflexive prosaccade tasks were used to allow comparisons of reflexive and intentional response latencies, and investigation of underlying causes of errors. It was important to strictly control the differences between the tasks, so that the influence of exogenous and endogenous components could be clearly assessed. To allow direct comparisons of response patterns the stimulus presentation in the prosaccade and antisaccade tasks was kept identical. To provide a clear comparison an immediate condition was chosen, instead of an overlap condition, for comparison with the gap condition. The only difference between the conditions was the insertion of the gap.

Table 3 Eye movement tasks with three fixation conditions and measures of interest in each task.

Task	Instruction	Abbr.	Measures of interest
Prosaccade tasks	Respond as fast as possible	IPS	Immediate prosaccade task Response latencies, proportion of express saccades.
		GPS	Gap prosaccade task Response latencies, proportion of express saccades. Gap effect.
	Delay response	DPS	Delayed prosaccade task Intentional control over reflexive and predictable intentional saccade production with stable fixation.
Antisaccade tasks	Respond as fast as possible	IAS	Immediate antisaccade task Proportion of errors, latencies of errors and correct antisaccades, proportion of express saccades.
		GAS	Gap antisaccade task Proportion of errors, latencies of errors and correct antisaccades, proportion of express saccades. Gap effect.
	Delay response	DAS	Delayed antisaccade task Intentional control over reflexive and predictable intentional saccade production with stable fixation.

1.6.3 Neuropsychological tests

Neuropsychological tests were chosen to assess abilities in five cognitive domains:

- Visuospatial perception
- Memory
- Problem solving
- Verbal fluency
- Working memory span and attention

Tests were selected to enable assessment of different working memory processes across cognitive domains. Some neuropsychological tests overlap in terms of content others overlap in terms of the type of processing required. Visuospatial tests were chosen that required only attentional selection and little cognitive processing. The problem solving task also involved visuospatial information, but the performance of this task required in addition to selective attention, manipulation of information and a degree of impulse control. The memory test involved learning and retrieval of items of verbal information, with optional manipulation of the information to facilitate task performance. Verbal information was also involved in the fluency tasks, but performance of these tasks depended on endogenous response generation and voluntary control over natural associations of generated words in favour of arbitrary task instructions. The tasks chosen to assess all aspects of working memory processing and attention required participants to maintain, retrieve and manipulate a number of items of information in working memory. The items were verbally presented digits, giving examinees the option to use verbal or visual strategies or a combination of both to perform the task.

1.6.4 The Tower of London task

In addition a task was chosen which allowed the recording of eye movements during cognitive processing. The aim was to assess directly the association between working memory processes and eye movements during a task requiring visuospatial processing. A sequence of Tower of London problems was selected reflecting varying levels of difficulty and complexity. The problems were designed for display on a computer monitor, so that eye movements could be recorded during the planning stage of the task.

2 Method

2.1 Ethics approval

Approval was sought from the Upper South A Regional Ethics Committee. Approval was granted, 4th August 2005, Ref : URA/05/04/034

2.2 Participants

Eye movement data and neuropsychological test scores of 19 patients and 18 control subjects were analysed for this study. Patients were selected from the Van der Veer Institute's database of PD patients. The diagnosis of idiopathic PD of the subjects in the PD group was confirmed by a neurologist (Prof. Tim Anderson). To prevent the inclusion of patients with dementia with Lewy bodies, patients with dementia were only included in the study if they had a history of movement disorders for at least 18 months prior to developing signs of cognitive decline. Hoehn &Yahr stages and Unified Parkinson's Disease Rating Scale (UPDRS) scores were obtained from the records of clinical assessments of the patients within 6 months of testing. Healthy control subjects, matching the patients in age and education level, were recruited from the Van der Veer Institute's database of volunteers and through a service agency for older people, Age Concern New Zealand.

2.2.1 Exclusion factors

Participants were excluded if they had a history of

- neurological impairment (apart from PD in the patient group)
- neurosurgery
- moderate or severe head injury or stroke
- major medical illness (e.g., cardiovascular disease, diabetes requiring the use of insulin, severe migraines)
- major psychiatric illness
- major depression in the last 6 months

Participants were also excluded if their (corrected) visual acuity was worse than 6/12

2.2.2 Subject demographics

Detailed description of participants with Parkinson's disease

Individual data for all PD participants, their medication and motor function is provided in Table 4 . A total of 28 participants with PD and 20 healthy control subjects were recruited. Neuropsychological data were collected for all participants. All subjects participated in an eye movement recording session. Technical problems prevented eye movement data collection in a number of cases. Bifocal lenses or characteristics of the eye, eye brows or eye lashes prevented the system from obtaining a recordable image of some participants' eye movements. Some of the participants in the PD group were unable to complete the eye movement recording due to tiredness, unstable posture or an inability to comply with the task requirements. Reliable eye movement data were recorded of 19 patients and 18 control subjects.

Details of all participants follow in Table 4 , Table 5 , and Table 6 .

No	H&Y	age	sex	MMSE	est IQ	Edu	FAQ	FAQ3s	yrs PD	UPDRS	medication	iView data
1	1	76	M	28	101	6	0	0	5	13	rotigotine	yes
2	1	62	F	28	118	8	0	0	5	21	sinemet, disipal, selegiline	yes
3	1	56	M	30	123	9	2	0	10	4	sinemet, pergolide, propanolol, doxazosin, prozac, selegiline	yes
4	1	64	F	28	100	4	2	0	9	6	sinemet, pergolide, disipal,	yes
5	2	59	M	30	92	7	1	0	9	29	sinemet, pergolide, amantadine, selegiline, benztropine, inhibace, domperidone	yes
6	2	73	M	28	120	9	0	0	4		pergolide, selegiline, sinemet	yes
7	2	75	M	30	113	4	0	0	2	21	none	yes
8	2	73	F	28	103	3	2	0	9		madopar, selegiline, atenolol, amitryptiline, imovane, calciferol	yes
9	2	54	M	30	123	9	0	0	10	22	disipal, dopergin, propanolol, sinemet, selegiline, amantadine	yes
10	2	66	F	30	107	4	4	0	10	7	madopar, pergolide, sinemet	yes
11	2	65	M	30	103	4	23	4	16		sinemet, selegiline, lipex, lisuride, coloxyl, domperidone	yes
12	2	66	F	28	113	9	3	0	5	33	sinemet, pergolide	yes
13	2	72	M	27	118	6	0	0	3	17	domperidone, lipex, cartia, amantadine, lisuride, cilazapril, frusemide, bezafibrate	yes
14	2	72	F	30	121	5	4	0	3	22	sinemet, citalopram, clonazepam	yes
15	3	65	M	30	117	6	7	0	20	30	sinemet, pergolide, selegiline, amantadine, omeprazole, orphenadrine	Prosaccades only
16	3	69	M	20	97	4	28	8	10	30	sinemet, clonazepam, entacapone, lisuride	Prosaccades only
17	3	45	M	30	101	8	0	0	15	16	sinemet, madopar, lisuride,	yes
18	3	73	M	23	111	4	24	6	6	28	madopar, pytazen, alopunol lipex, quetiapine, flixotide,	yes
19	3	65	M	28	107	4	17	0	15		sinemet lisuride	yes
20	3	64	M	30	106	2	4	0	2	45	sinemet, lisuride, nitrofurantoin	Too tired, unstable posture
21	3	67	M	30	120	3	0	0	8		sinemet, selegiline, amantadine, pergolide	Glasses, small pupil
22	3	79	F	18	107	6	6	0	5		sinemet, oxybutynin, fluoxetine, aspirin	Too tired
23	3	73	M	26	105	3	6	0	7	24	pergolide, bendrofluazide, lipex, madopar, enalapril maleate, aspirin, atenolol	Pupils small and hidden by eye lids
24	4	78	M	23	96	3	21	4	9		midodrine, sinemet, aspirin, osteo, etidronate, quinine sulphate, metoprolol, lipex, domperidone	Too tired
25	4	77	M	30	115	6	16	2	15		selegiline, sinemet, vaxol, miniram	Dyskinesia
26	4	71	M	27	112	3	2	0	29		sinemet, oxybutynin, aspec, pergolide, orphenadrine, selegiline, horinef	Eyes closing during trials
27		62	M	29	120	12	1	0	8			Bifocal glasses
28		78	M	30	122	9			5		rotigotine, atenolol, sinemet, benztropine	Pupils small, eyes red and tired

Table 4 Details of participants with Parkinson's disease

Table 5 Details of all healthy control subjects

No	age	sex	MMSE	Est IQ	Edu	FAQ	BDI	iView data (yes/no)
1	54	M	30	121	10	0	0	yes
2	59	M	30	116	5	0	5	yes
3	60	F	30	123	10	0	0	yes
4	61	F	29	120	12	0	0	yes
5	62	M	29	110	7	0	3	yes
6	63	F	30	118	4	0	0	yes
7	64	F	29	111	3	0	2	yes
8	64	M	30	120	8	0	16	yes
9	65	M	30	127	5	0	0	yes
10	67	M	29	100	9	0	0	yes
11	68	M	30	111	6	0	6	yes
12	69	M	30	125	9	0	3	yes
13	69	M	29	108	5	0	6	yes
14	70	M	30	116	3	0	2	yes
15	72	F	30	127	8	0	5	yes
16	72	F	30	127	12	0	0	yes
17	77	M	30	126	7	0	4	yes
18	79	M	29	116	10	0	6	yes
19	75	F	30	117	10	0	1	No, tracking impossible, pupil was not visible enough
20	76	F	28	121	7	0	7	No, tracking impossible due to glasses

Table 6 Mean values (± S.D.) of demographics of the participants who provided eye movement data.

Group	Parkinson's patients			Healthy control subjects		
Sex	F	M	all	F	M	all
Mean age	66.6 (4.9)	65.3 (10.0)	65.7 (8.6)	65.3 (4.8)	66.9 (6.8)	66.3 (6.2)
Number	6	13	19	6	12	18
Est IQ	110 (8.4)	110 (10.3)	110 (9.3)	121 (6.1)	116 (8.1)	118 (7.65)
Education	5.5 (2.4)	6.08 (1.98)	5.89 (2.1)	7.83 (3.6)	6.92 (2.3)	7.22 (2.7)
MMSE	28.67 (1.0)	29.67 (3.14)	28.21 (1.11)	29.67 (0.5)	28.00 (0.5)	29.66 (0.06)

2.3 Eye movement trials

2.3.1 Apparatus

Eye movements were recorded using the video-based iView X Hi-Speed system. This system consists of a tracking column, containing the camera and an infrared light source. One PC was used to run the eyetracking system and another PC to generate the presentation of the stimuli. Stimuli were presented on a computer monitor, 500mm in front of the subject who sat with head supported by the chin/forehead rest of the tracking column See 0.

The iView X Hi-Speed is a pupil and corneal reflection tracking system using infrared light and computer based image processing. At a sampling rate of 240 Hz the video image allows the eye tracking system to record coordinates for the centre of the pupil and the corneal reflection.

Stimuli were generated by the custom developed 'Experimenter' software, which allowed the accurately timed presentation of images on the computer screen. Durations of display events could be specified with accuracy in the range of 2-4 ms. Images were generated in Photoshop. The Experimenter software also embedded stimulus events in the form of text messages into the eye tracking data stream. This guaranteed the accurate coordination of gaze data and the temporal sequence of the stimulus presentation.

iView X tracking column and the display monitor

2.3.2 Analysis of eye movement data

All gaze data were stored on the iView PC for offline analysis. Customised software was developed to display target onsets and display and analyse the contingent eye movement responses. Dependent measures were based on latency, velocity, duration, and gaze position of saccades in response to target onsets. If a response consisted of more than one saccade the primary as well as subsequent saccades were described. Eye movement measures and visual display parameters were combined in a spreadsheet for statistical analysis.

For each trial the saccadic responses were selected semi-automatically. Two types of variables were collected for analysis. Time related data are expressed relative to target onsets. Data describing eye position (gaze location) are expressed relative to the central fixation stimulus (with negative numbers relating to locations to the left and positive numbers relating to locations to the right of the centre). Variables available for analysis included:

- Latency of the first saccade initiated after target onset (time elapsed between target onset and the initiation of the response) expressed in ms. The initiation of a saccade was identified by the software. When the software detected a sample with a very high velocity (indicating a saccade in progress), it then searched backwards from there to find the first preceding sample at which the velocity was < 5 deg/s (indicating saccade start).
- Duration of the primary saccade (time elapsed between start and finish of the first saccade after target onset) expressed in ms. The finish of a saccade was identified by the first instance of 0 deg/s velocity after saccade initiation.
- Amplitude of the primary saccade (the distance between the initial eye position and the position of the eye at the finish of the first saccade) in pixels

- Initial eye position (position of the eye at the start of the primary saccade) in pixels
- Mid position (position of the eye after the primary saccade) in pixels
- Final eye position (position of the eye after the final saccade) in pixels

If a response consisted of more than one saccade (e.g., an erroneous saccade and a corrective saccade) the first saccade was measured as above and the corrective saccade was measured with additional variables. The variables used to measure the corrective saccade included:

- Latency of corrective saccade relative to target onset expressed in ms.
- Eye position at the start of the corrective saccade in pixels
- Eye position after the primary corrective saccade in pixels
- Final eye position in pixels

Error classification

All eye movement responses were classified as either correct or incorrect. Responses on prosaccade and antisaccade tasks can either be directionally correct or incorrect. Responses on delayed trials can either be temporally correct or incorrect. In the antisaccade tasks responses in the direction of the target were classed as directional errors. In the delayed tasks responses initiated before fixation point offset in the delayed tasks were classed as timing errors. Prosaccades initiated before fixation point offset, in the direction of the target in the delayed antisaccade task were classed as 'timing and directional' errors. Errors were further classed as corrected or not corrected, depending on whether a secondary, corrective saccade followed the initial response to the same target appearance.

Anticipatory responses and express saccades

Based on the latency of the primary saccade, all responses were also classified into anticipatory, express or normal saccades. Definitions of express saccades vary in the literature. Some investigators define express saccades as all visually guided saccades with latencies between 90 and 140 ms (Armstrong et al., 2002; Chan et al., 2005), while others use a range of 85 to 135 ms (Biscaldi et al., 1996) or between 80 and 130 ms (Fischer et al., 2000). In this study no saccades with latencies below 90 ms were included in the final analysis. This number was chosen to ensure that no anticipatory responses were inadvertently included. An analysis of reflexive responses at very short latencies revealed that, in our study, approximately 50% of saccades with latencies

below 70 ms were made in the direction away from the target. This indicated that subjects anticipated target onset and initiated a response before the target was presented. Interestingly, between 70 and 90 ms after target onset no control subject made a saccade away from the target, but in the PD group 25% of these responses were still in the opposite direction from the target. In the prosaccade tasks, at latencies longer than 90 ms all responses were towards the target in both groups. The upper limit of 140 ms was decided on the basis of responses in the antisaccade task with a gap condition. On the antisaccade tasks only 0.5% of responses with latencies below 140 ms were saccades away from the target. Therefore we were confident that saccades with latencies between 90 and 140 ms were fast reflexive (express) saccades.

2.3.3 Procedure

Each participant was asked to attend one morning session at the Van der Veer Institute. The participants in the PD group were instructed to take their medication as usual on the testing day and to bring along any medications that they required during the morning. A session lasted between 2.5 and 3.5 hours. Testing started with an explanation of the procedures and signing of the consent form. This was followed by a semi-structured interview to establish rapport and gather relevant information on medication, medical history, educational background and lifestyle. The eye movement trials took between 45 minutes and 1.5 hours, depending on the ease and success of the calibration procedure. If the subject was coping well with the procedures and no technical problems occurred the Tower of London tasks were presented after the saccade trials. After a break of 15 minutes, during which a cup of tea or coffee was offered, the session continued with the remaining neuropsychological tests.

2.3.4 Eye Movement Tasks

Calibration

The iView X system was calibrated before each recording. The calibration procedure required the subject to fixate a sequence of 13 reference targets on the subject monitor, which were used to map pupil and corneal reflection coordinates to gaze locations on the monitor. Success of the calibration procedure depended on a stable fixation at each location. After a successful calibration eye movements were tracked by the iView system and the point of gaze was displayed on the operator monitor. To check the validity of the calibration procedure an image consisting of 9 targets of known locations was displayed simultaneously on the subject and the operator monitors. The subject was then asked to fixate the targets on the subject monitor allowing the investigator to check

the display of the gaze position on the operator monitor. If the point of gaze displayed on the operator monitor matched the gaze position of the subject the recording started.

Self-paced task

The first eye movement task presented after successful calibration was a self-paced task. Two targets were presented for 30 seconds on the monitor at 13 deg to the left and right of the centre of the monitor. The colour of the targets was green (R0 G254 B0) and the colour of the background was grey (R143 G155 B164). The size of the targets was 10 x 10 pixels, subtending 0.75 deg at 500 mm distance from the monitor (One pixel was 0.625mm in size on the monitor). The instruction to the subject was: “Please move your eyes as quickly and accurately as possible between the two targets, going backwards and forwards between the targets from the time they appear on the monitor until they disappear”.

Saccade trials

The self-paced task was followed by blocks of saccade trials. A trial consisted of the display of a fixation point in the centre of the subject monitor followed by the appearance of a peripheral target either to the left or the right of the centre. A trial finished with the peripheral target’s offset and the reappearance of the central fixation point. The fixation point, target stimuli and background were as in the self-paced task.

Blocks of trials

A block of trials consisted of the presentation of 24 peripheral targets. Potential target locations were at 8, 10.5 and 13 degrees to the left or the right of the central fixation point. The duration of the display of the central fixation stimulus before target onset could be 1800, 2000, 2200 or 2400 ms. The sequence of target presentation and the duration of the display of the fixation stimulus were pseudo-randomised. Each target location was used four times in one block of trials. Target stimuli were always displayed for 1000 ms.

Conditions

Trials were presented in three different conditions. Each block of trials contained 24 trials of the same condition. In the *immediate* condition the fixation point offset coincided with target onset. In the *gap* condition fixation point offset occurred 200 ms before target onset. In the *delayed* condition fixation point offset occurred 400 ms after target onset.

Tasks

A total of six blocks of trials was presented. On the first three blocks of trials the participants were asked to make *prosaccades*. On the other three blocks they were asked to make *antisaccades*. The *immediate*, *gap* and *delayed* conditions were each presented once for each type of task. The stimulus presentation for the prosaccade and antisaccade trials was identical. The tasks only differed in the instructions to the participant. See 0 for an illustration of the stimulus presentation.

Instructions

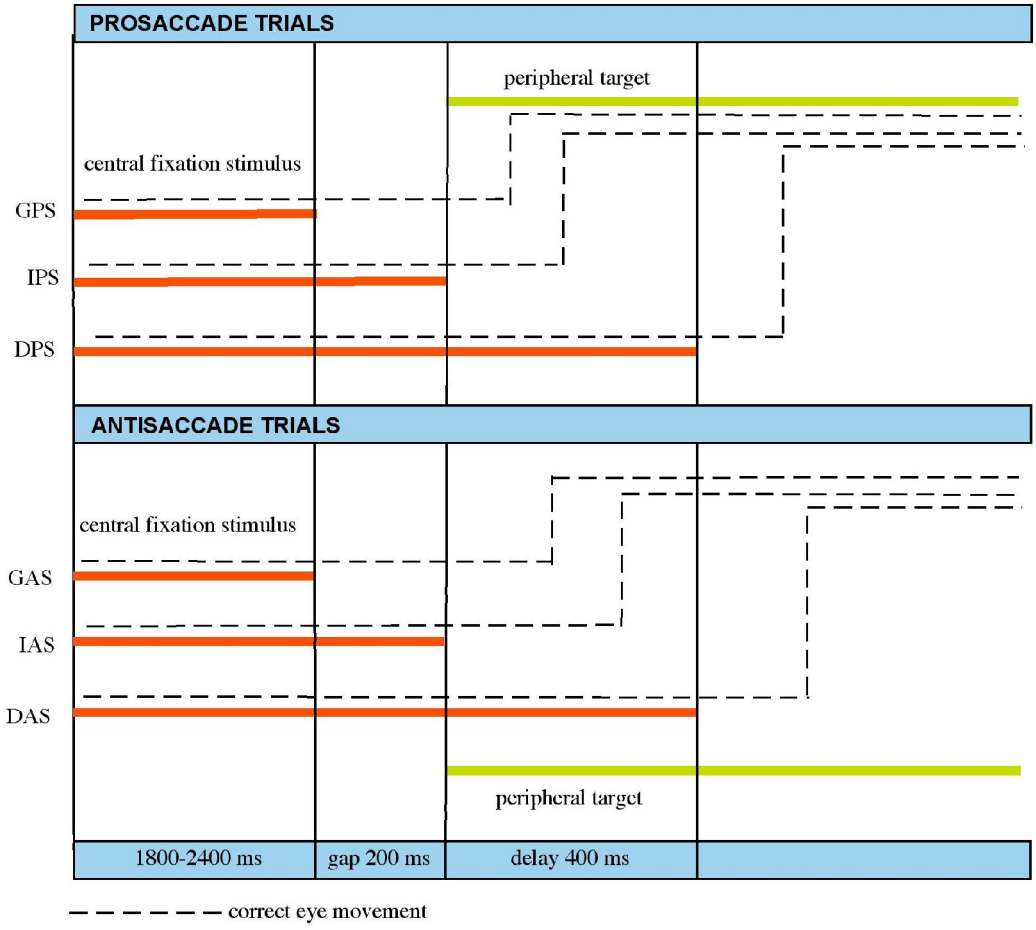
The instruction to the participants for the prosaccade task in the gap and immediate conditions was: “Your task is to fixate the red square in the centre and to move your eyes as quickly and accurately as you can towards the green square when it appears”. For the delayed condition of the prosaccade task the instruction was: “In the next sequence we will do something different. Now the red square will stay on when the green square appears. Your task is to try and wait for the red square in the centre to disappear before you move your eye as quickly and accurately as you can towards the green square”.

For the antisaccade task in the gap and immediate conditions the instruction was: “Now we will do something different again. I will show you exactly the same squares, but this time your task is to move your eye in the opposite direction from the green square. Try not to look at the green square when it comes on, but move your eyes to a mirror position of the square, an equal distance from the centre, but in the opposite direction”. These verbal instructions were followed by a manual demonstration pointing out a hypothetical target and the direction of an antisaccade on the blank screen in front of the subject. The subject was then given the opportunity to ask questions if not totally sure about the task. For the delayed condition of the antisaccade task the instruction to the subject was: “In the next trials the red square will stay on when the green target appears. Your task is to wait until the red square in the centre disappears and then move your eyes in the opposite direction, away from the green square”. The participant was again given an opportunity to ask for clarification if not absolutely clear about the task, before the next block of trials was presented.

Order of trial presentation

The order of the presentation of the six blocks was fixed. The test started with the three blocks of prosaccade tasks, followed by three blocks of antisaccades. Within the tasks the order of conditions was also fixed. The immediate condition was presented first, then

the gap condition, and finally the delayed condition. The presentation of tasks and the abbreviations used to identify the tasks is shown in Table 7 .



Stimulus presentation and correct eye movements on prosaccade and antisaccade trials in three conditions.

Table 7 Table of the order of presentation and the abbreviations used for the tasks

Eye movement task			Fixation condition and eye movement measures
Prosaccades	1	IPS	Immediate: fixation point offset and target onset temporally coincide Response latency was measured from target onset. Only saccades towards the target stimulus were analysed.
	2	GPS	Gap: fixation point offset occurs 200 ms before target onset. Response latency was measured from target onset. Only saccades towards the target stimulus were analysed.
	3	DPS	Delay: fixation point offset occurs 400 ms after target onset Response should not be initiated before fixation point offset. Latency of correct response was measured from fixation point offset. Only saccades towards the target stimulus were analysed. Saccades initiated before fixation point offset were counted as errors.
Antisaccades	4	IAS	Immediate: fixation point offset and target onset temporally coincide. Response latency was measured from target onset. Saccades in the direction of the stimulus were counted as errors.
	5	GAS	Gap: fixation point offset occurs 200 ms before target onset. Response latency was measured from target onset. Saccades in the direction of the stimulus were counted as errors.
	6	DAS	Delay: fixation point offset occurs 400 ms after target onset Response should not be initiated before fixation point offset. Latency of correct response is measured from fixation point offset. Saccades in the direction of the stimulus initiated before fixation point offset were counted as 'timing and direction' errors, saccades initiated after fixation point offset in the direction of the stimulus were counted as direction errors, antisaccades initiated before fixation point offset were counted as timing errors.

2.4 Neuropsychological Testing

2.4.1 Tests

If a relative of a patient was available at the time of the testing session he or she was asked to fill in the Functional Activities Questionnaire (FAQ). If no relative was present the FAQ forms were posted out to the participant's home address to be filled in and returned by mail.

Following the semi-structured interview at the beginning of each testing session, each participant filled in the Beck's Depression Inventory (BDI-II) questionnaire. The Mini Mental State Exam (MMSE) was then administered. Additional neuropsychological tests were administered in the following order (the selection of tests has been informed by research undertaken by Audrey McKinlay):

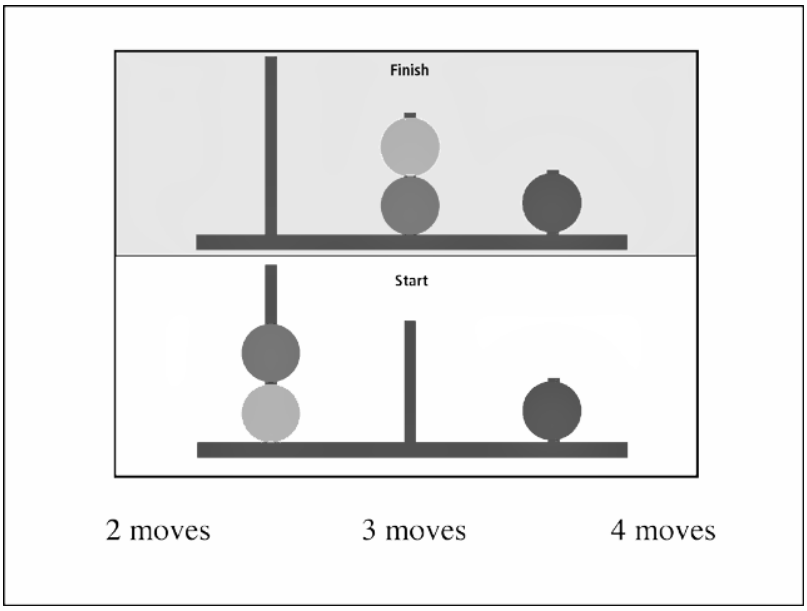
- California Verbal Learning Test: CVLT-Short Form (acquisition and short delay),
- Screening and incomplete letters of the Visual Object and Space Perception Battery (VOSP),
- Benton Judgement of Line Orientation-Form H (JLO)
- CVLT-Short Form (long delay),
- Delis Kaplan Executive Function System - Letter Fluency (D-KEFS)
- Action Fluency Test (AFT),
- Wechsler Abbreviated Scale of Intelligence (WASI) Matrix Reasoning Test
- Wechsler Memory Scale (WMS-III) Digits Forwards, Digits Backwards
- Digit Ordering Test (DOT-A)
- National Adult Reading Test (NART).

2.4.2 Test Scores

The tests were scored manually on paper. Raw scores were adjusted for age and sex according to guidelines provided in test manuals. For ease of comparison across tests scores were converted to z-scores, based on means and standard deviation of normative data provided by the test manuals. The z-scores were then converted to T-scores with the formula $T = 10*z + 50$. (T-scores have a normal distribution with a mean of 50 and a standard deviation of 10) These T-scores were used for statistical analysis between groups and comparison with eye movement data. The obtained scores allowed comparisons between the PD and the control groups.

2.5 Tower of London

The subjects were asked to plan the number of moves required to solve the Tower of London problem, while their eye movements (scanpaths) were recorded with the iView system. Problem selection was based on insights from previous studies (Kaller et al., 2004; Unterrainer et al., 2004). 0 shows one of the items of the Tower of London task adapted for display on the iView monitor.



One of the practice items of the Tower of London task, adapted for display on the iView monitor (image adapted from Audrey McKinlay's version of the Tower of London task)

A set of four practice items was presented to familiarise the participant with the task and the mouse button. Subsequently the system was recalibrated if necessary and the session continued with the first set of six test items. No feedback was given apart from encouragement to guess the answer when a participant was taking longer than one minute to think about a solution. If the participant was able and willing to continue the second set of six problems was presented. The subject indicated with a mouse press when the planning stage of the task was finished, and subsequently provided the answers verbally. The answer consisted of the estimated number of moves required to solve the problem and the colour of the ball of the first move. Iview recorded all eye movements during the planning stages of the problems. The answers were typed into the iView datastream by the investigator.

3 Results

The results for the comparison of the Parkinson's disease and control group are presented in tables below. First eye movement measures and the effects of task and fixation condition in each group are presented. Then the scores for the neuropsychological tests in each group are given, followed by the investigation of potential associations between the eye movement and cognitive data sets. To be able to compare the results of the current study with previous eye movement studies of groups of non-demented PD patients, two PD patients who met clinical criteria for dementia (PD-D) were excluded from the analysis.

3.1 Eye movement data

A short description of each eye movement task is provided Table 7 , together with the abbreviations referring to the six different tasks and the measures obtained for the analysis in each task and condition.

Prosaccade tasks

In each of the three conditions of the prosaccade task the mean latency of all correct responses was calculated for each subject. Responses with latencies shorter than 90 ms were excluded. The proportion of saccades with latencies between 90 – 140 ms (% express saccades) was calculated as a percentage of all correct responses. In the delayed condition of the prosaccade task the proportion of responses initiated before fixation point offset was also calculated (% timing errors). The results are presented in Table 8 as a function of fixation condition.

Prosaccade latencies and gap effects

Over the three different conditions a main effect of fixation condition on prosaccade latency was found, $F(2,98) = 37.10$, $p<0.00001$. The mean latencies for each group in each condition are shown in Table 8 . Overall the difference between the latency of responses in the gap condition and the immediate condition of the prosaccade task was 42 ms (the gap effect). The gap effect was larger in the PD group (53 ms) than in the control group (32 ms), but the difference was not statistically significant ($p = 0.06$). No main effect of group or interaction of group and fixation condition was found.

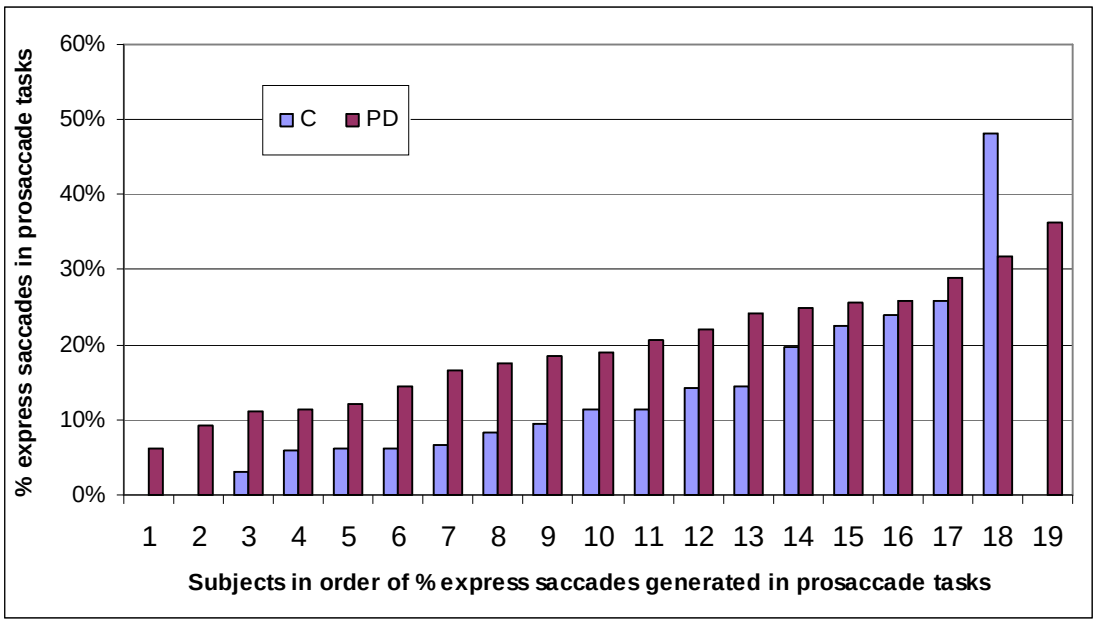
Table 8 Mean values (± S.D.) of latencies of correct responses and the proportion of express saccades and errors for the Parkinson's (PD) and control (C) groups as a function of condition (gap, immediate or delay) in the prosaccade tasks.

Prosaccade tasks	Latency (ms)	% express saccades	% errors
Gap condition (GPS)			
PD	157 (±20)	48 (±21)	n/a
C	165 (±34)	34 (±24)	n/a
Immediate condition (IPS)			
PD	210 (±53)	8 (±7)	n/a
C	197 (±26)	6 (±10)	n/a
Delayed condition (DPS)			
PD	280 (±93)	8 (±11)	42 (±24)*
C	263 (±64)	5 (±11)	20 (±21)

* Difference between PD and control groups was statistically significant at $p<0.05$

Proportion of express saccade generated in prosaccade trials

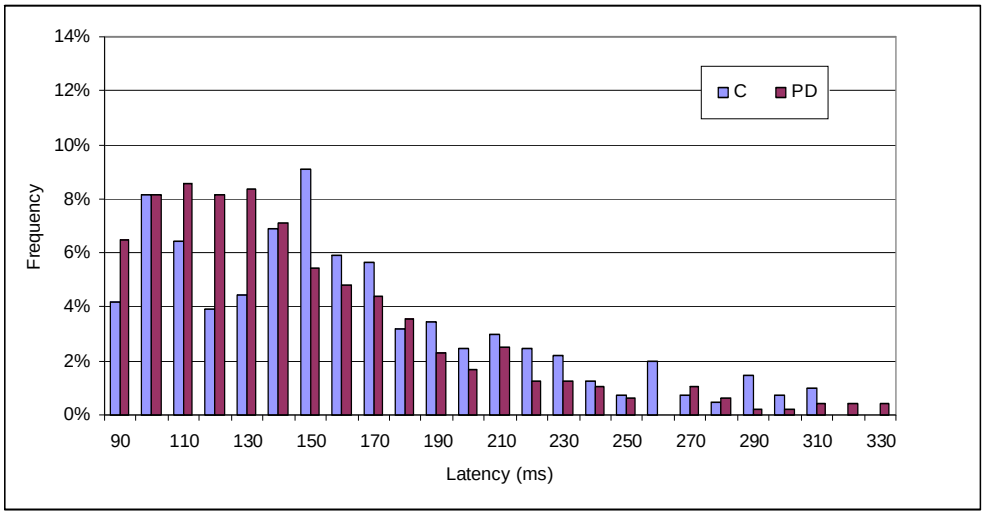
There was a main effect of fixation condition on express saccade production, $F(2,98) = 60.10$, $p<0.0001$. The gap condition elicited an average of 41%, the immediate condition 7% and the delay condition 6% express saccades. On average the PD group generated more express saccades (21%) than the control group (15%) on prosaccade trials. This difference failed to reach statistical significance, $F(1, 98) = 3.90$, $p = 0.051$. The proportion of express saccades generated by each participant in the prosaccade tasks is shown in 0. Only four subjects in the control group, but nine in the PD group produced express saccades on more than 20% of the prosaccade trials. The control group contained one subject who produced express saccades on 48% of all prosaccade trials. This score had a large influence on the outcome of the statistical comparison of express saccade proportions. No interaction between group and fixation condition was found.



Proportion of express saccades generated by each subject on the prosaccade tasks, ranked in ascending order. One of the control subjects had a very high score on this measure.

Distributions of response latencies in the prosaccade task with a gap

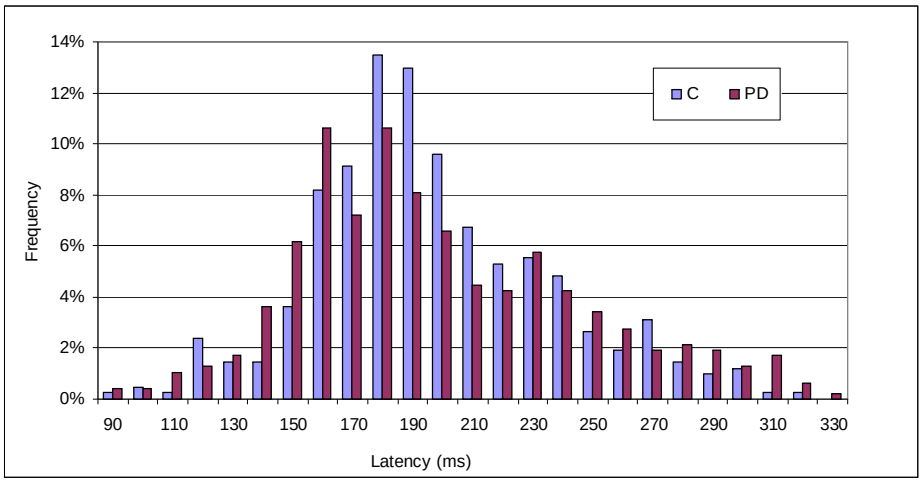
0 shows the frequency distribution of the latencies of all saccadic responses in the PD and control groups in the gap condition of the prosaccade task. Mean latencies did not differ between the groups, but the distributions of the latencies show some differences. Response latencies in the control group follow a bimodal distribution, with the first peak around 105 ms and the second peak around 150 ms. Frequencies of response latencies in the PD group do not follow the same distribution pattern. The latencies in this group form a skewed distribution, with latencies in the range of express saccades (90 –140 ms) more likely in the PD group than in the control group. The PD group made express saccades on 48% and the control group on 34% of trials in the gap condition. This difference failed to reach statistical significance, $p = 0.07$.



Frequency distribution of all response latencies of PD and control subjects in the gap condition of the prosaccade task. The distribution of latencies in the control group is bimodal, while the distribution of latencies in the PD group is unimodal.

Distributions of response latencies in the immediate condition of the prosaccade task

0 shows the frequency distribution of response latencies in the immediate condition of the prosaccade task. In this condition the latencies form mainly unimodal distribution patterns in both groups, with a possible trend towards a second peak at 180 ms in the PD group.



Frequency distribution of all response latencies of PD and control subjects in the immediate condition of the prosaccade task. In this condition the distributions are unimodal in both groups.

Antisaccade tasks

In each condition of the antisaccade tasks the mean latency of all correct and the mean latency of all incorrect responses was calculated for each subject. Only responses with latencies over 90 ms were included in the analysis. The proportion of responses with latencies between 90 – 140 ms (% express saccades) was calculated as a percentage of the total number of responses. The proportion of erroneous prosaccades (% errors) was

calculated as a percentage of the total number of responses. Most erroneous prosaccades were followed by corrective antisaccades in both groups (100% of errors were corrected in the control group and 99.5% in the PD group). The results are presented in Table 9 as a function of fixation condition.

Latencies in the antisaccade tasks

Latencies obtained from the delayed antisaccade task were left out of this analysis, as they can not be compared directly to the latencies in the gap and immediate conditions. A main effect of group on latencies of correct antisaccades was found: 316 ms in the PD group and 277 ms in the control group, $F(1,97) = 5.09$, $p = 0.03$. Also a main effect of fixation condition on latencies was found. The mean latency of correct antisaccades in the gap condition was 287 ms and in the immediate condition 340 ms, $F(1,97) = 7.23$, $p = 0.002$. No interaction of group and fixation condition was found.

Error rates in the antisaccade tasks

Overall the PD group made more errors (37%) in the three antisaccade tasks than the control group (22%), $F(1,97) = 11.16$, $p = 0.001$. In the delayed condition of the antisaccade task the directional error rate was significantly lower (20%) than in the immediate and gap conditions (both 34%), $F(2,97) = 4.23$, $p = 0.02$. No interaction between the effects of group and fixation condition was found.

Proportion of express saccades generated in antisaccade trials

The proportion of responses at latencies between 90 and 140 ms (% express saccades) was significantly higher in the antisaccade task with a gap condition (19%) than in the immediate (4%) or delayed (5%) conditions of the antisaccade task, $F(2,97) = 17.92$, $p < 0.00001$. No interaction between effects of group and fixation condition was found.

Latency of directional errors on the antisaccade tasks

A main effect of fixation condition on the mean latency of directional errors was found. The mean latency of errors was 165 ms in the gap condition and 235 ms in the immediate condition, $F(1,59) = 19.058$, $p=0.0005$. No interaction between the effects of group and fixation condition was found.

Table 9 Mean values (± S.D.) of latencies of correct responses and the percentage of express saccades and errors for the Parkinson's (PD) and control (C) groups as a function of condition (gap, immediate or delay) in the antisaccade tasks.

Antisaccade tasks	Latency correct responses (ms)	Latency error responses (ms)	% express saccades	% errors
Gap condition (GAS)				
PD	314 (±79)*	159 (±51)	24 (±20)	39 (±23)
C	262 (±50)	171 (±57)	16 (±18)	26 (±23)
Immediate condition (IAS)				
PD	355 (±99)	231 (±63)	4 (±7)	41 (±24)
C	325 (±82)	241 (±81)	3 (±6)	25 (±22)
Delayed condition (DAS)				
PD	274 (±131)	315 (±188)	4 (±6)	23 (±23)
C	246 (±65)	326 (±173)	5 (±11)	14 (±18)
Average over GAS and IAS				
PD	334*	195	14	43*
C	293	206	9	26

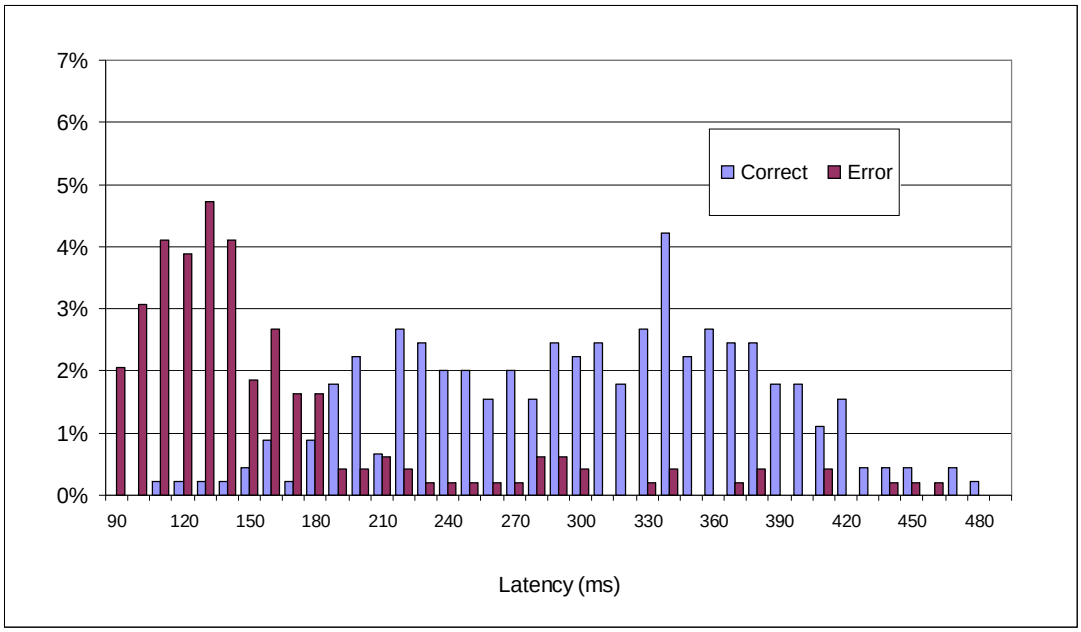
* Difference between PD and control groups was statistically significant at $p<0.05$

Distributions of the latencies of directional errors and correct antisaccades

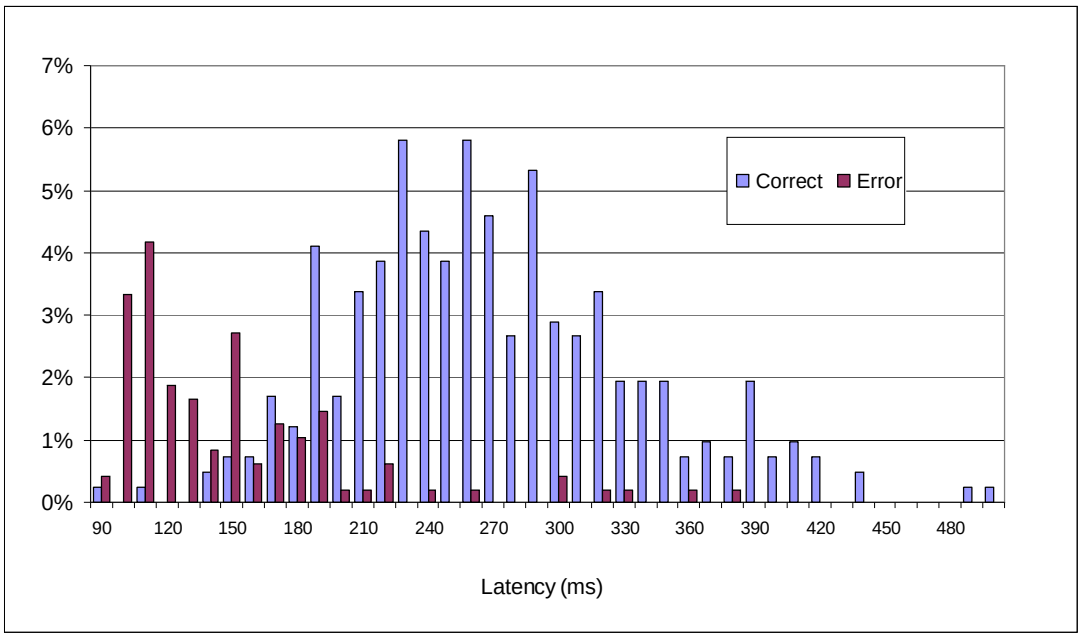
The frequency distributions of responses in the antisaccade tasks show that many of the errors are made at short latencies in both groups (see 0, 0, 0, and 0). The effect of the gap on latencies of directional errors was reliable, latencies of the directional errors were on average 70 ms shorter in both groups. The gap had no effect on the proportion of directional errors in either group.

The shape of the distributions of directional errors in the antisaccade task with a gap resembles the shape of the distributions of response latencies in the prosaccade task with the same fixation condition in both the PD and the control groups. A sharp reduction in responses after 115 ms after target onset occurs in the control group in the prosaccade and the antisaccade task (erroneous reflexive responses). This sharp fall in reponses at this latency is absent from the distribution of latencies in the PD group, both in the gap condition of the prosaccade task and the antisaccade task.

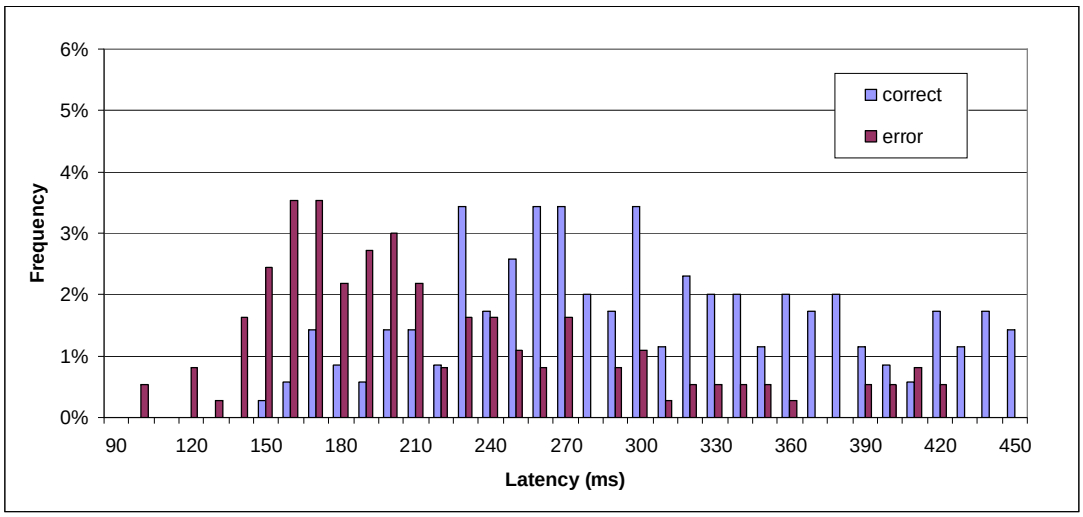
The latencies of correct antisaccades of the control group in the antisaccade tasks form unimodal distributions. In contrast, latencies of correct antisaccades in the PD group are spread over a wider range of values, without clear modes in the distribution.



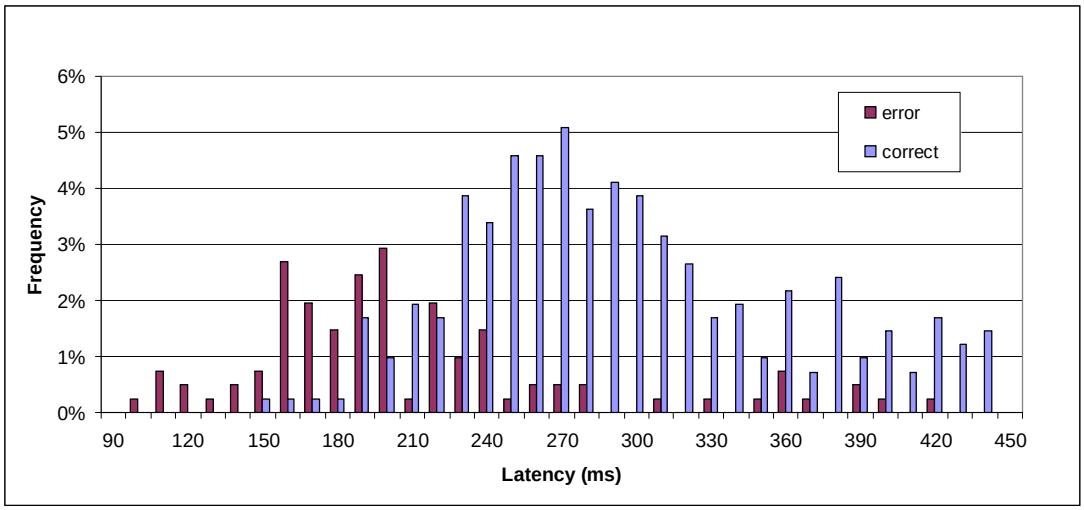
Frequency distribution of latencies of directional errors and correct antisaccades in the gap condition in the PD group.



Frequency distribution of latencies of directional errors and correct antisaccades in the gap condition in the Control group.



Frequency distribution of latencies of directional errors and correct antisaccades in the immediate condition in the PD group. The distribution does not show any clear modes.



Frequency distribution of latencies of directional errors and correct antisaccades in the immediate condition in the control group. Latencies of the correct antisaccades form a unimodal distribution around 270 ms.

Delayed prosaccade and antisaccade tasks

A main effect of task on error rate was found. In the delayed prosaccade task the mean error rate was 31%, and in delayed antisaccade task the mean total error rate was 20%, $F(1,64) = 4.35$, $p = 0.04$. No interaction between the effects of group and task was found.

The PD group made significantly more timing errors in the delayed prosaccade task than the control group, 42% and 20% respectively, $p = 0.007$.

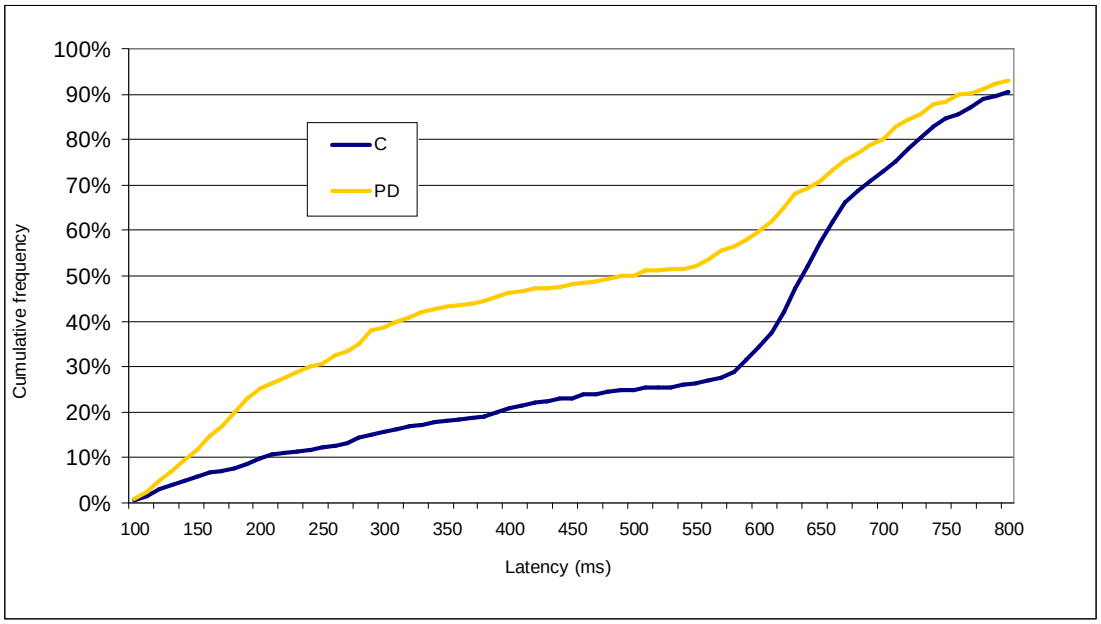
Three types of errors were identified in the delayed antisaccade task. Table 10 shows the proportions of each error type made in each group. No significant differences between the groups were found on the individual measures.

Table 10 Mean values (±S.D.) of the proportion and type of errors in the delayed antisaccade task (DAS)

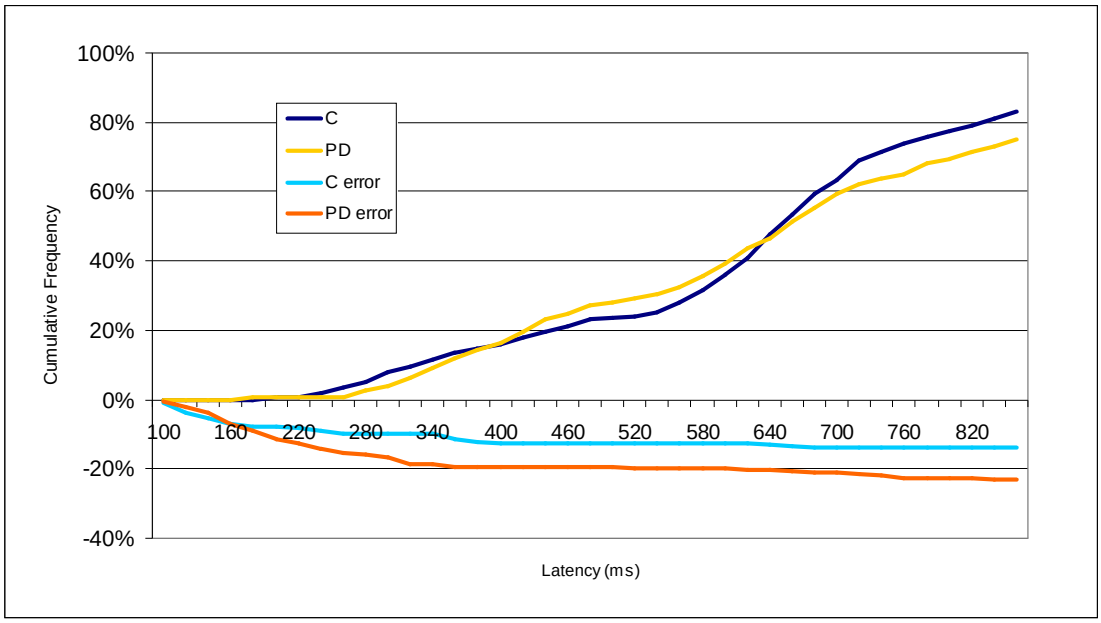
Group	Timing & direction	Timing	Direction	Total direction	Total errors
PD	20 (±23)	14 (±13)	3 (±3)	23	37 (±20)
C	12 (±18)	16 (±19)	2 (±3)	14	30 (±27)

The cumulative frequencies of response latencies in the delayed tasks are shown in 0 and 0. Target onset occurred at 0 ms and fixation point offset at 400 ms. For the delayed prosaccade task all prosaccade responses are shown. In the delayed antisaccade chart all antisaccades are shown above the x-axis and erroneous prosaccades are shown below the x-axis. In both tasks responses initiated before 400 ms are timing errors.

Many of the timing errors in the PD group are made at short latencies. In the control group a steep rise in the response rate occurs after 575 ms (175 ms after fixation point offset). This effect is attenuated in the PD group.



Cumulative frequencies of prosaccades in the delayed condition in the PD and the control groups. Prosaccades initiated before fixation point offset (at 400 ms) are errors. A steep rise in responses occurs in the control group 170 ms after fixation point offset.



Cumulative frequencies of correct antisaccades and directional errors in the delayed condition in the PD and the control groups. Antisaccades initiated before fixation point offset (at 400 ms) are timing errors. Erroneous prosaccades are shown below the x-axis.

Effect of task on express saccade and error response generation

The effect of the fixation condition on the generation of express saccades is modulated by task instruction. Table 11 shows the effect of task instruction on the generation of express saccades in both groups. While express saccades are correct responses in the prosaccade tasks, all express saccades are errors in the delayed tasks and almost all are errors in the antisaccade task (more than 99%). Overall more express saccades were

produced in the prosaccade tasks (18%) compared to the antisaccade tasks (9%), $F(1, 203)=11.890$, $p < 0.0001$. The PD group had a tendency to make more express saccades than the control group (16% vs 11%), $F(1, 203)=3.6084$, $p = 0.058$. However, the groups were equally able to suppress a proportion (approximately 50%) of their express saccades in the antisaccade trials.

Table 11 Proportions of express saccades (%) modulated by fixation condition and task in each groups.

Fixation condition	**Gap**		**Immediate**		**Delay**	
Task	GPS	GAS	IPS	IAS	DPS	DAS
PD	48	24	8	4	8	4
C	34	16	6	3	5	5

3.2 Tower of London task

Data from the eye movement recording during the Tower of London task were not analysed. Firstly, the dropout rate was considerable with many PD patients not able to complete the task for various reasons. Tiredness, and unstable posture were the main PD related factors preventing the collection of reliable data. Secondly, available software was not suitable for the amount of data to be analysed and for the level of accuracy required. Collected data are stored for potential future analysis.

3.3 Neuropsychological test scores

Individual test scores were adjusted for age and sex differences according to guidelines provided in test manuals. The resulting scores were rated relative to norms provided and standardised. The resulting T-scores have a mean of 50 and a S.D. of 10 and indicate if a specific score is at, below or above the expected score for a subject of the same sex and similar age. The PD group scored lower than the control group on many of the neuropsychological tests. The scores for two participants who met criteria for dementia were not included in this analysis. Table 12 lists the mean score and S.D. on each test for each group.

Table 12 Mean test scores (± S.D.) for all neuropsychological tests for the Parkinson's disease group and healthy control group, adjusted for age and sex according to test guidelines and converted to T-scores (Mean = 50 and S.D. = 10)

Domain	Test	PD group	Control group
Visuospatial perception	VOSP -2	56.05 (±4.33)	56.19 (±3.46)
	LOJ	54.42 (±6.76)*	59.52 (±3.39)
Memory	CVLT (Acquisition)	52.71 (±9.27)*	62.89 (±11.00)
	CVLT (short delay)	55.00 (±10.60)*	63.88 (±9.78)
	CVLT (Long Delay)	54.12 (±9.88)*	60.28 (±6.52)
	CVLT (Recognition)	51.18 (±3.76)	50.28 (±6.75)
Verbal fluency	D-KEFS - Letter fluency	55.69 (±13.27)	62.04 (±10.01)
	Action Fluency	51.95 (±9.76)	56.44 (±4.97)
Problem solving	WASI Matrix Reasoning	57.06 (±9.14)*	65.00 (±4.78)
Working memory	Digits Backward	37.67 (±11.92)*	46.64 (±12.40)
	Digits Ordering Test	44.96 (±14.36)	50.65 (±10.23)

* Difference between PD and control groups was statistically significant at $p<0.05$

Average neuropsychological scores

Average scores in each of the five domains were calculated from the main scores within each domain. VOSP-2 and LOJ scores were averaged to obtain the score for 'visuo-spatial perception'. CVLT (acquisition) and CVLT (long delay) scores were averaged to obtain the score for 'memory'. Letter and action fluency scores were averaged to obtain the score for 'verbal fluency'. The WASI matrix reasoning score was used as the score for 'problem solving'. The score for 'working memory' was obtained by averaging the scores from the Digits Backward and the Digit Ordering Tests. Finally a total average neuropsychological score was calculated from the five domain scores. The resulting scores are shown in Table 13 .

Table 13 Mean test scores (± S.D.) for five cognitive domains for the Parkinson's disease group and healthy control group. Scores are averages of main component scores in each domain.

Domain	PD group	Control group
Visuo-spatial perception	55.23 (±4.54)*	57.85 (±2.51)
Memory	53.41 (±8.51)*	61.58 (±7.55)
Verbal fluency	53.82 (±10.06)	59.24 (±6.16)
Problem solving	57.06 (±9.14)*	65.00 (±4.78)
Working memory	41.31 (±11.45)*	48.65 (±8.78)
Average Total Cognitive Score	53.66 (±6.87)*	59.65 (±3.92)

* Difference between PD and control groups was statistically significant at $p<0.05$

3.4 Associations between cognitive scores and eye movement measures

Potential associations of abnormal eye movement measures and cognitive deficits were explored with multivariate data exploration. A factor analysis with principle components extraction was performed of the scores of all PD participants (excluding two PD-D patients) on the main variables from the oculomotor and cognitive tests. The results are presented in Table 14 . Three factors were identified, explaining 72% of the variance in the data set:

Factor 1. Cognition

Factor 2. Proportion of directional errors

Factor 3. Intentional saccade latencies

The proportion of timing errors in the delayed prosaccade task loaded onto Factor 1, the same factor as the cognitive tests (with an opposite sign). Reflexive saccade latencies loaded onto Factor 2, the same factor as the proportion of directional errors (with an opposite sign).

Table 14 Factor analysis of the data of the PD group (excluding controls and PD-D patients). Loadings > 0.70 are marked in bold.

	Factor 1	Factor 2	Factor 3
GPS latency	0.18	**0.72**	0.51
IPS latency	-0.13	0.29	**0.77**
GAS latency	-0.06	-0.19	**0.86**
IAS latency	-0.20	-0.11	**0.90**
% Directional errors DAS	0.48	0.22	-0.18
% Timing errors DAS	-0.13	0.58	0.02
% Timing & direction errors DAS	-0.49	-0.64	-0.06
% Directional errors IAS	-0.25	**-0.80**	-0.05
% Directional errors GAS	0.12	**-0.90**	0.15
% Timing errors DPS	**-0.72**	0.20	-0.26
% Express saccades on PS tasks	-0.31	-0.54	-0.13
% Directional errors on AS tasks	-0.10	**-0.95**	0.09
Visuo-spatial perception	**0.75**	-0.09	-0.03
Memory	**0.79**	0.37	0.08
Verbal fluency	**0.73**	0.01	-0.01
Problem solving	**0.85**	0.15	-0.48
Working memory	**0.80**	0.02	-0.17
Average cognitive score	**0.93**	0.20	-0.38
Explained Variance	5.84	4.39	4.55
Proportion total	0.29	0.21	0.22

Correlations between eye movement measures and cognitive test scores

Non-parametric analysis was performed to explore specific associations between cognitive measures and eye movement data. The results for the Spearman Rank Order test for all participants are shown in Table 15 . Exploration of the relative strength of associations was the main goal of the analysis; a p-level of 0.01 was chosen to indicate significance. The proportion of timing errors on the delayed prosaccade task is negatively associated with the memory (-0.73) and visuo-spatial perception (-0.58) scores. The latency of correct responses on the antisaccade task is negatively associated

with the working memory score (-0.66). The proportion of directional errors in the antisaccade task was not significantly associated with any of the cognitive test scores.

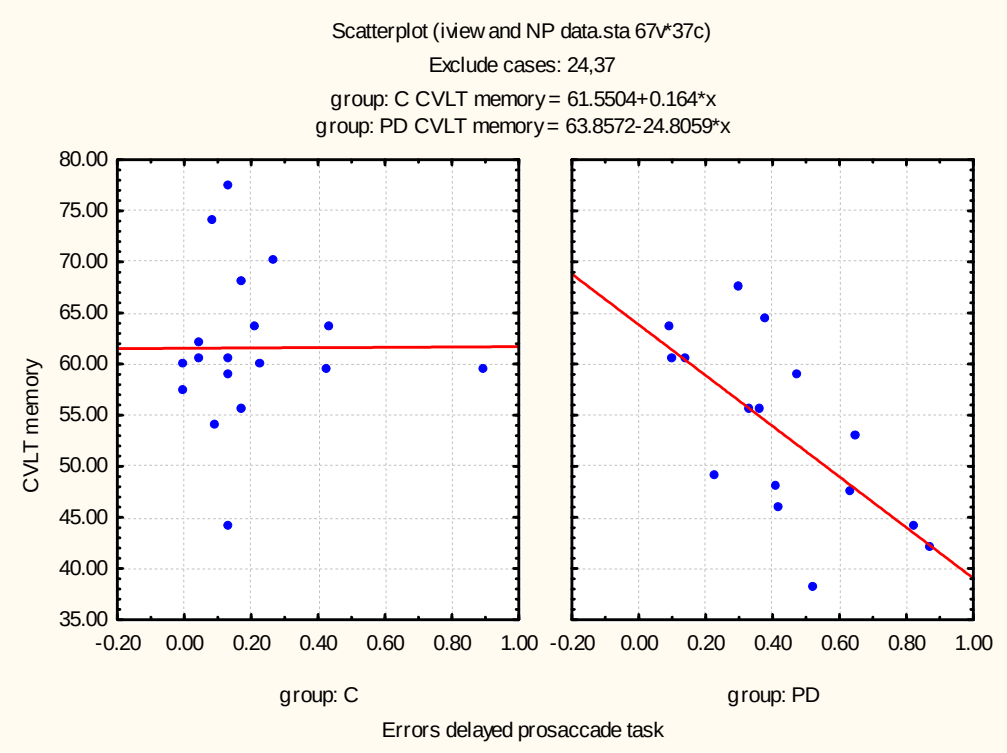
Table 15 Spearman Rank Order correlations between the cognitive scores and saccadic latencies and error rates for PD group only (excluding PD-D subjects). Correlations significant at p< .01 are shown in bold.

	Visuo-spatial perception	Memory	Verbal fluency	Problem solving	Working memory
GAS latency	-0.09	-0.24	-0.31	0.20	-0.30
IAS latency	-0.25	-0.05	-0.32	-0.12	**-0.66**
% timing errors DPS	**-0.58**	**-0.73**	-0.30	-0.31	-0.42
% express saccades on GPS task	-0.35	-0.02	-0.20	-0.21	-0.30
% directional errors on AS tasks	-0.45	-0.16	-0.29	0.05	-0.31

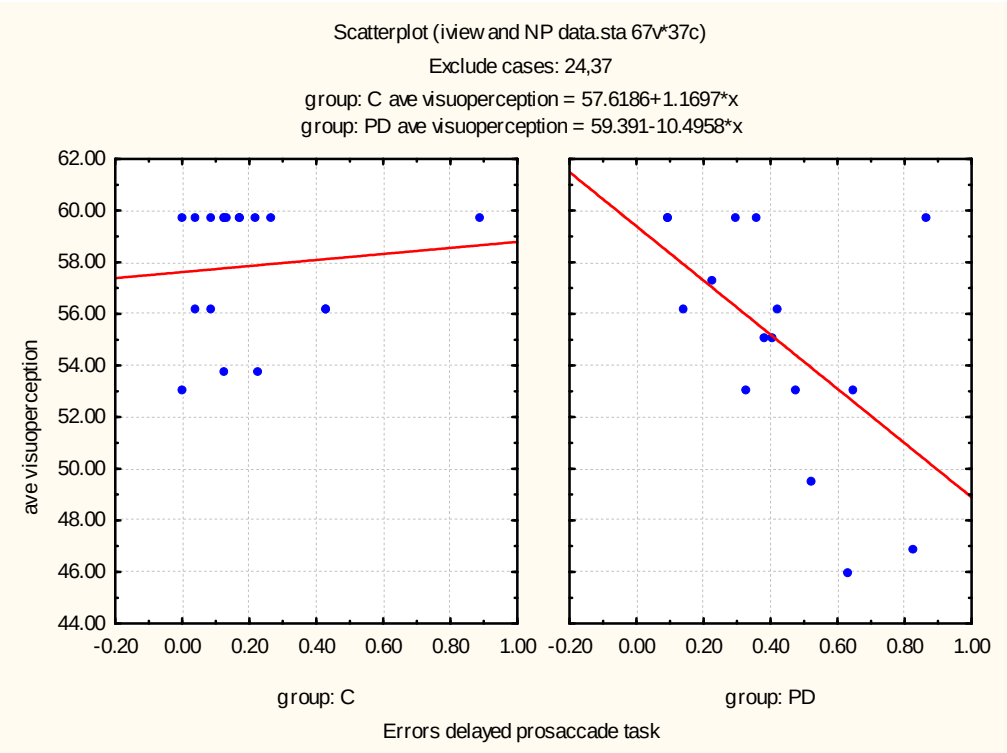
The association between the proportion of timing errors in the delayed prosaccade task and the CVLT-memory score was not present in the healthy control group. The different associations are illustrated in 0 and 0. PD patients who made more than 30% of timing errors in the delayed prosaccade task were likely to have low scores in the memory test and the visuospatial perception tests.

PD patients who made correct antisaccades at latencies longer than 350 ms were likely to have a low working memory score as illustrated in 0.

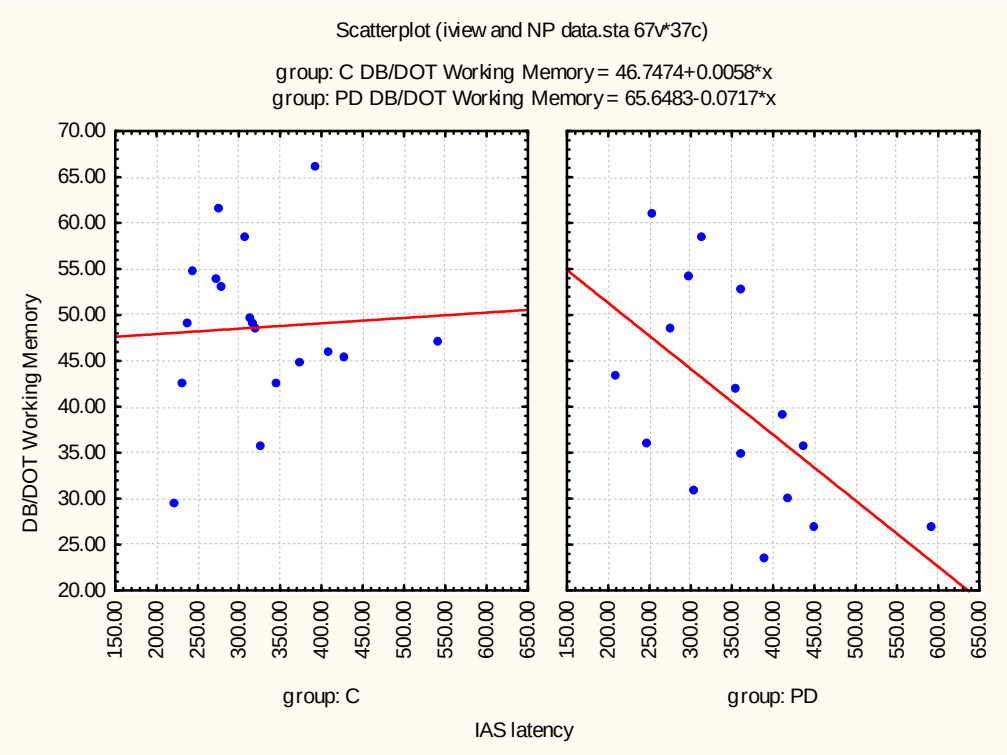
0 shows that the proportions of timing and directional errors are not associated with each other in PD. Patients who made more than 30% timing errors in the delayed prosaccade task were not likely to also make an increased proportion of directional errors in the antisaccade task.



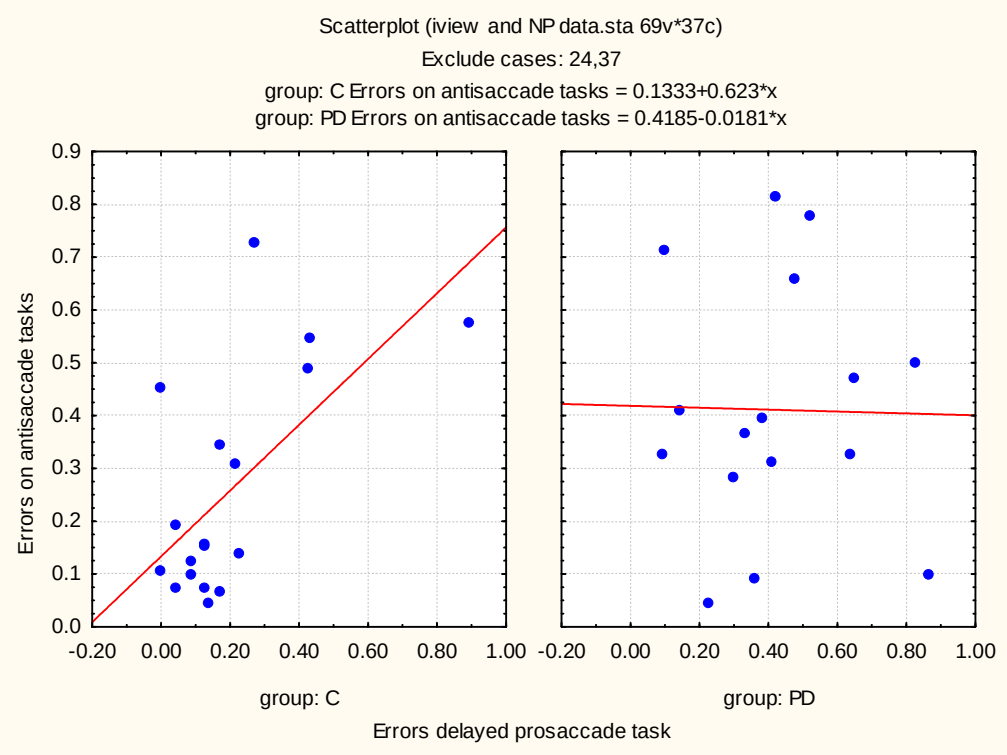
Association of the proportion of timing errors in the delayed prosaccade task and memory scores in the PD and the control groups. Lower scores on the memory test are associated with larger proportions of timing errors on the delayed prosaccade task in the PD group only.



Association of the proportion of timing errors in the delayed prosaccade task and visuospatial perception scores in the control and the PD groups. Lower scores on the visuospatial perception tasks are associated with higher proportions of timing errors on the delayed prosaccade task in the PD group only.



Association of antisaccade latencies and working memory scores in the control and the PD groups. Lower scores on the working memory tests are associated with longer antisaccade latencies in the PD group.



Association of the proportion of timing errors in the delayed prosaccade task and the proportion of directional errors in the antisaccade task in the PD and the control groups. The subjects in the PD group who make timing errors on a large proportion of the trials in the delayed prosaccade trials, do not necessarily also make more directional errors on antisaccade trials and vice versa.

4 Discussion

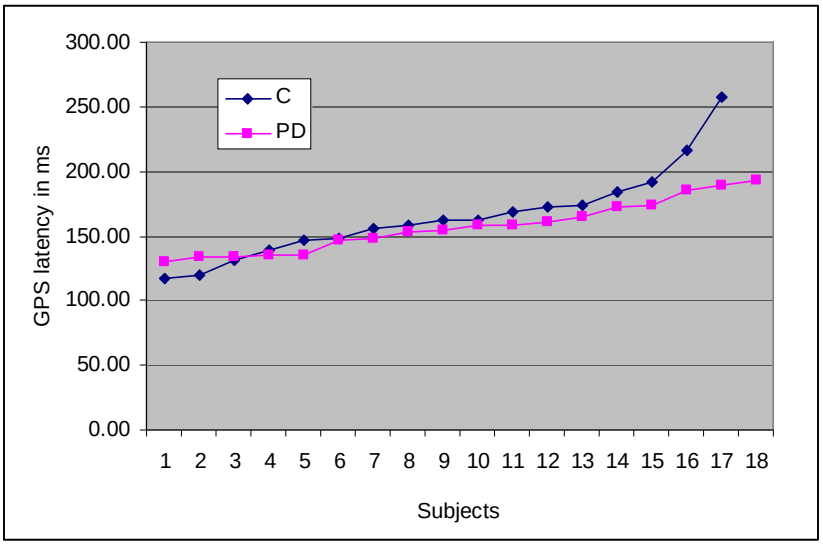
This chapter will first present a discussion of the differences found between the groups. The evidence for associations of abnormal oculomotor control and cognitive deficits will then be assessed. The findings from this study will be discussed in relation to conclusions from other studies. In the final section of this chapter the limitations and potential for future extensions of the current study will be discussed.

4.1 Eye movement control

The main interest of the investigation was to assess intentional eye movement control of patients with PD and clarify the nature of any deficits by exploring associations with cognitive impairments of the PD patients. The measures of interest were latencies of reflexive saccades, proportion of express saccades produced, latencies of intentional saccades and the proportion of errors as a measure of failed reflexive response inhibition. Statistically significant differences between the PD and the control groups were found in three aspects of eye movement control.

Latencies of reflexive saccades

Previous research had reported conflicting results regarding the latencies of reflexive saccades in groups of PD patients. Reflexive saccades were either found to be normal or to have faster latencies than normal in the patient groups. The current study did not find evidence of different mean latencies for reflexive saccades in the PD group compared to the control group.



Average reflexive saccade latencies in the gap condition of individual subjects in the PD and the control groups, ranked in ascending order. The average latencies are similar in the PD and control groups.

The issue of the putative faster reflexive responses was investigated further by calculating the proportion of express saccades generated by each subject. This measure proved to be a valuable tool reflecting the different shapes of the frequency distributions of reflexive saccade latencies in the gap condition in the two groups (see 0).

Overall, the difference in the proportions of express saccades generated in the prosaccade tasks in each group (21% v 15%) failed to reach statistical significance, p=.051. However, nine PD patients made express saccades on more than 20% of prosaccade trials compared to only four subjects in the control group. The increased frequency of responses occurring at very short latencies indicates that the triggering of saccades by visual information can be facilitated in PD.

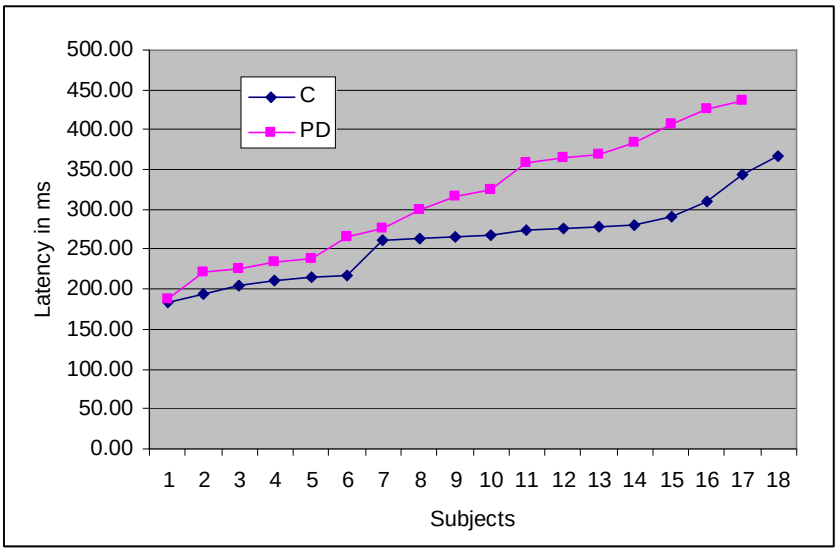
The finding of normal average latencies together with an increase in express saccade production may explain why some studies reported faster reflexive responses in PD patients (Briand et al., 2001; Chan et al., 2005; Kingstone et al., 2002) and other studies decided that reflexive response latencies are normal in PD (Briand et al., 1999; Mosimann et al., 2005; Shaunak et al., 1999; Stuyven et al., 2000). On average latencies of reflexive saccades in PD may be normal, but the distribution of latencies and the number of express saccades reveal differences between the groups.

Counting the number of express saccades in each task and condition also provided a measure of the ability to voluntarily suppress the triggering of these fast reflexive saccades. Subjects in the PD group generated express saccades on 48% of trials in the gap condition of the prosaccade task. This proportion was reduced to 24% in the gap condition of the antisaccade task, where reflexive responses would have been errors. The reduction was entirely due to the different task instruction, as the stimulus presentation in the two tasks was identical. Interestingly, the control group reduced their proportion of express saccades to a similar extent, from 34% in the prosaccade task to 16% in the antisaccade task. These results suggest that triggering of saccades is facilitated in PD, that the likelihood of reflexive saccades being triggered can be voluntarily reduced, and that the neural mechanism underlying this reduction is intact, at least in some PD subjects.

Slower generation of antisaccades

The finding that PD patients in the current study generated antisaccades at significantly longer latencies than controls is consistent with the results of recent studies (Amador et al., 2005; Chan et al., 2005; Crevits et al., 2004). Earlier reports had found evidence for normal antisaccade latencies in mild to moderate cases of PD (Kitagawa et al., 1994; Lueck et al., 1990) and longer antisaccade latencies in more severe cases (Crevits et al.,

2000; Kitagawa et al., 1994; Mosimann et al., 2005). In the current study disease severity was not associated with longer antisaccade latencies. 0 shows that some PD patients have quite normal average antisaccade latencies, while others are significantly slower than subjects in the control group. This divergence of average latencies may have affected the statistical results of studies with small experimental groups.



Average latencies of antisaccades in the gap condition of individual subjects in the PD and the control groups ranked in ascending order. Some patients generate antisaccades at latencies similar to subjects in the control group, but others are substantially slower.

Directional errors in the antisaccade tasks

The PD group made more directional errors in the antisaccade tasks than the control group. This result is consistent with reports in the literature (Amador et al., 2005; Briand et al., 1999; Chan et al., 2005; Crevits et al., 2000). However, the proportions of directional errors in the gap condition of the antisaccade task in Chan's study are much lower than the proportions found in the current study (in Chan et al.: 19% in PD v 9% in controls, and in the current study: 40% in PD v 25%). Differences in design between the two studies may have contributed to the different numbers of errors. Participants in Chan et al.'s study performed 240 antisaccade trials, while the current study only presented 48 antisaccade trials. A practice effect has been observed previously in antisaccade tasks (Everling & Fischer, 1998) and may therefore reduce the proportion of directional errors when more trials are presented in a single session. This may also explain why the proportion of errors reported in Chan et al.'s study in the delayed condition of the antisaccade task (PDs: 20% and controls: 5%) is actually higher than in their overlap condition (PDs: 14% and controls: 4%). The gap and overlap conditions were presented in one session, but the delayed conditions of the prosaccade and the antisaccade task

were presented in a separate testing session on a different day. A smaller number of trials in the delayed tasks may have reduced the practice effect.

The proportions of errors generated in the current study are similar to the proportions reported by Amador et al. (2005): 40% and 25% for the PD and control groups respectively in the current study, and 44% and 18% for the PD and control groups in Amador's study. The proportions of errors generated in the delayed condition of the antisaccade task were also similar in the two studies: 21% and 13% for the PD and control groups respectively in the current study, and 24% and 9% for the PD and control groups in Amador's study. This indicates that in the current and in Amador's study both groups could reduce the likelihood of producing a reflexive error by about 50%, when instructed to delay an intentional response, when a central fixation point remains visible during the trial. Intentional fixation on this fixation point automatically suppresses saccade related activity and prevents reflexive saccades from being triggered. The results suggest that some PD patients are as capable as control subjects to use intentional fixation to delay a predictable antisaccade.

Timing errors in the delayed prosaccade task

Previous investigations of delayed response tasks have consistently found deficits in PD (Amador et al., 2005; Chan et al., 2005). The PD patients in the current study made significantly more timing errors (responses initiated before fixation point offset at 400 ms after stimulus onset) than the control group (42% v 20%). These proportions are similar to the numbers reported by Chan et al. (2005) in the same task: 41% and 19%. The delayed prosaccade task challenges the ability to maintain stable fixation during the 400 ms delay while a reflexive response is suppressed and an (identical) predictable response is delayed. The significantly larger proportion of timing errors in the PD group suggests that in some patients the ability to maintain stable fixation in these circumstances is impaired.

Inspection of the relevant correlations in Table 16 revealed that subjects in the PD group who made numerous directional errors in the antisaccade tasks did not necessarily also make a large proportion of timing errors in the delayed prosaccade task. The proportions of the two error types were not associated with each other (r=.20). In contrast, PD patients who made numerous directional errors in the antisaccade tasks were more likely to make express saccades in the prosaccade tasks (r=.65) The propensity to generate express saccades was only weakly associated with the proportion of timing errors in the delayed prosaccade task (r=.36). (For the full matrix see Appendix 2)

In summary, the current study found that on average PD patients made reflexive saccades with normal mean latencies. However, PD patients were more likely than the control subjects to make express saccades. The propensity to make such fast reflexive responses was associated with a larger number of directional errors in the antisaccade tasks. Overall the subjects in both experimental groups were able to voluntarily reduce the production of unwanted reflexive saccades (including express saccades) by approximately 50% when required in the antisaccade and delayed saccade tasks. But individual ability to control unwanted responses depended partly on the task: the proportions of timing errors in the delayed prosaccade task were not associated with the proportions of directional errors in the antisaccade task. Latencies of antisaccades were longer in the PD group on average, but a divergence was seen between subjects with normal and slower than normal latencies within the PD group.

In the next section the additional information from the neuropsychological tests will be assessed in relation to the results from the eye movement tasks.

4.2 Neuropsychological test scores

While many participants scored above average in the neuropsychological tests, the group of PD patients in this study contained a number of patients who scored more than 0.6 S.D. below the expected average scores on several components of the neuropsychological test battery. The scores within the PD group were therefore spread over a wider range than the scores in the control group. The components that were most sensitive to a loss of cognitive ability in the group of PD patients were the memory (CVLT), working memory (digits backward and digit ordering tests), and problem solving (WASI matrix reasoning) tests. The verbal fluency task was not as sensitive to different cognitive abilities of the PD subjects as the other tasks.

4.3 Associations of cognitive scores and measures of oculomotor control

Next, the question was explored whether deficits in the cognitive tests were associated with any of the abnormalities of eye movement control found in this group of PD patients. The production of express saccades and the proportion of directional errors in the antisaccade tasks were found to be associated with each other, but not with any of the cognitive test scores. In contrast, the proportion of timing errors was negatively associated with the memory score ($r=-.73$) and the antisaccade latency with the working memory score ($r=-.66$).

Table 16 Spearman Rank Order Correlations of oculomotor measures and cognitive measures in the PD group. The proportion of express saccades is associated with directional errors, the proportion of timing errors is associated with lower memory scores and antisaccade latency is associated with lower working memory scores. Correlations shown in bold are significant at p<.01

	% express saccades	% direction errors	Memory	Verbal fluency	Problem solving	Working Memory	UPDRS
IAS latency	0.03	0.33	-0.05	-0.32	-0.12	**-0.66**	0.36
% timing errors DPS	0.36	0.20	**-0.73**	-0.30	-0.31	-0.42	0.09
% direction errors	**0.65**	1.00	-0.16	-0.29	0.05	-0.31	0.48

These results are consistent with the findings of Roberts, Hager and Heron (1994) and Kitagawa, Fukushima and Tashiro (1994). Roberts et al. found that working memory span was associated with antisaccade latencies and not with directional error rates in a group of healthy young subjects. Kitagawa et al. also found a dissociation between the proportion of directional errors and antisaccade latencies. In that study, the generation of increased numbers of directional errors was found to be associated with the use of anticholinergics, while the longer antisaccade latencies in advanced PD patients were associated with more errors on the Wisconsin Card Sorting Test.

In the current study the associations of eye movement measures and cognitive tasks that were found appear to reflect common use of basic working memory processes in the tasks. Longer antisaccade latencies were associated with a lower score for working memory derived from the Digits Backwards and Digit Ordering tasks. The antisaccade and the neuropsychological tasks both involve manipulation of information in working memory for their correct performance. In the antisaccade task the spatial coordinates for the direction and amplitude of the response have to be calculated by a manipulation of visuospatial information provided by the stimulus.

An association was also found of the proportion of timing errors in the delayed prosaccade task and the score for memory as assessed with the short version of the CVLT. Stable maintenance of information in working memory is a prerequisite for the suppression of reflexive saccades in the delayed tasks as well as for the efficient performance of the memory task. The associations found in this current study are consistent with findings by Holthausen (2003) who investigated eye movements and neuropsychological test performance in schizophrenia, in relation to putative frontal lobe

deficits. Directional errors in the antisaccade task were found to be associated with a measure of psychomotor speed, while errors in a delayed response task were associated with a CVLT-derived memory score.

4.4 Evidence for an impaired voluntary system in PD?

Investigators over the last couple of decades have tried to find a unified hypothesis to explain 'the Parkinsonian saccadic deficit' (Lueck et al., 1992). Several investigators have suggested that the specific pattern of deficits of oculomotor control found in groups of PD patients is consistent with the notion of a general impairment of the voluntary system in PD e.g.,(Amador et al., 2005; Armstrong et al., 2002; Chan et al., 2005; Crevits & De Ridder, 1997). This general impairment is assumed to be associated with a dysfunction of striatal-basal ganglia-prefrontal circuitry. The next section will evaluate the results from the current study in relation to this hypothesis.

Implicit in the suggestion that PD is associated with a general impairment of the voluntary system, is the assumption that increased express saccade production, timing and directional errors and prolonged intentional saccade latencies have a common pathological cause. From our results, however, it appears that for some of the PD patients at least there is no reason to assume that the voluntary system is dysfunctional. Some PD patients were capable to prevent a substantial proportion of unwanted reflexive responses, when a task demanded an intentional response. An alternative explanation may also be consistent with the apparent deficit of response control in these patients. It may be that the (intact) voluntary system is unable to exert normal control over response production, due to a change in the acceleration and deceleration of firing rates of neurons in the SC. Noise in the signal or bursting of neural discharges may disturb normal response control by increasing the chances that a visual stimulus will trigger a saccade (e.g., Trappenberg et al., 2001). Overall the inhibitory influence over this system can be increased voluntarily, consistent with the lower numbers of express saccades occurring in tasks that engage the intentional system. This would indicate that abnormal response control is not necessarily evidence for impaired prefrontal-striatal connections. Our data suggest that antisaccade latencies may be more sensitive to impairment of frontal-striatal processes than the number of reflexive errors.

Models of eye movement control

Different models of eye movement control make different predictions regarding the effects of pathology on error rates and latencies in oculomotor tasks. Three models of eye movement control will be discussed in relation to the current study.

Sereno's (1992) model of tonic inhibition is based on the notion that the reflexive system is controlled by a tonic inhibitory output from the voluntary system (thought to include prefrontal-basal ganglia circuits. Reflexive errors are interpreted as evidence for impairment of the voluntary (inhibitory) system. Amador et al.(2005) interpret their results in relation to this model. However, it is difficult to differentiate between cause and effect in this model. Longer response latencies and increased numbers of errors would be predicted to have a common cause according to this theory.

Roberts et al.'s model of inhibition assumes that suppression of reflexive responses depends on the availability of working memory resources. The ability to inhibit unwanted responses diminishes when resources are diverted to concurrent tasks or when working memory processes (thought in this model to reside in prefrontal neural structures) are damaged (Roberts, 1994). This model is silent on the actual mechanism involved in the inhibitory signal. This model would not predict that fewer express saccades are produced in antisaccade tasks compared to prosaccade tasks with the same stimulus conditions.

The parallel processing model of saccade programming (Massen, 2004; Mokler & Fischer, 1999) is based on the notion that reflexive and intentional components of saccade production operate concurrently rather than subsequently as assumed in other models. This model suggests that errors in the antisaccade task occur when the reflexive pathway triggers a saccade before the intentional component is fully activated. It predicts that increased production of directional errors will be associated with faster than normal reflexive responses or slower than normal developing intentional responses or a combination of both factors. The suggested mechanism involved in voluntary suppression of reflexive responses depends on mutually inhibitory interactions between the intentional and reflexive pathways.

The parallel processing model predicts that if the gap condition decreases the latencies of both reflexive and intentional saccades, the likelihood that the reflexive pathway will trigger an unwanted saccade before the intentional pathway can initiate the wanted saccade remains the same. This model is consistent with the results in the current study., While the gap affected latencies of errors as well as correct antisaccades, the gap did not affect the proportion of errors in the antisaccade task in either group.

Chan et al. suggest that their results are consistent with a general deficit of automatic saccade suppression, associated with a disorder of prefrontal-basal ganglia circuitry in PD. This impairment of the frontal-basal ganglia circuit may release the saccade system (the SC in particular) from inhibition and cause a deficit in the functioning of the

intentional component of the saccade system. This interpretation does not clarify which component of the saccadic system is responsible for abnormal oculomotor control in PD. It is difficult to justify the attribution of increased proportions of directional and timing errors to a common cause, if the two types of errors are not made by the same subjects.

The results of the current study suggest that different neural mechanisms may be involved in different aspects of abnormal eye movement control in PD. One mechanism causes faster reflexive responses and another mechanism is responsible for longer latencies of antisaccades. Previous results with the antisaccade task in PD may have been mixed because these two mechanisms affect both components of the antisaccade task. Only by looking at different errors and distributions of latencies can these issues be clarified and teased apart.

Longer latencies are a separate issue from express saccades and errors. In some patients the benefits from the increase in activity in the SC is negated or counterproductive and intentional movements are slowed. In these patients neurodegeneration may have affected areas beyond the BG DA system. In others there is no reason to assume a prefrontal deficit when increased directional error rates are found.

4.5 Limitations and suggested extensions of the current investigation

The current investigation found evidence of abnormal oculomotor control and cognitive impairments in a group of PD patients. As the purpose of the investigation was to clarify the potential existence of an association of deficits of eye movement control and cognitive impairment, the recruitment of patients was biased towards the inclusion of patients with a wide range of cognitive abilities. The evidence of cognitive deficits cannot be considered to generalise to other groups of PD patients.

The findings of the investigation are constrained by the necessarily limited selection of oculomotor and cognitive tasks presented. One important condition used in previous eye movement investigations, but omitted in the current study was the overlap condition. It was thought important to avoid confusion by keeping the instruction to 'respond on fixation point offset' constant in all eye movement tasks. It was also thought that the comparison between the gap and immediate condition would be clearer than between the gap and the overlap condition as explained in 1.6. However, the addition of an overlap condition would have added relevant information regarding the endogenous release of fixation related activity and its effect on response latency and error production.

Another aspect of the design of the present study that may limit the generality of the findings is the fixed order of presentation of the tasks. Priority was given to presenting the tasks in a fixed order from the easiest prosaccade task to the most complex delayed antisacade task to minimise confusion of patients who may have had trouble understanding and following the task instructions. However, it can be argued that by presenting the immediate condition of the antisaccade task before the gap condition a learning effect may have eliminated or attenuated a difference in the proportion of directional errors. In future investigations these issues could be addressed.

Future investigations of cognitive processes and eye movement control would benefit from the comparison of the performance of eye movement tasks that depend on a particular type of working memory process. Oculomotor tasks involving maintenance of information in working memory could be compared with tasks involving stable fixation. For instance it may be interesting to compare the performance of memory guided saccades and delayed prosaccades. Tasks involving manipulation of information in working memory could be compared with antisaccade performance. Visual search tasks involving decisions or combinations of features for target selection could be compared to antisaccade performance.

Finally, future studies could also address the influence of medication on specific working memory operations. It has been suggested that L-dopa may have different effects on the performance of task requiring mainly stable maintenance of information and on tasks depending mainly on shifting or updating of information in working memory (Cools et al., 2003). These different effects may be relevant to the performance of oculomotor tasks, in particular the delayed response and the antisaccade tasks.

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