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Deficits in saccadic eye-movement control in Parkinson's disease

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Abstract

In contrast to their slowed limb movements, individuals with Parkinson's disease (PD) produce rapid automatic eye movements to sensory stimuli and show an impaired ability to generate voluntary eye movements in cognitive tasks. Eighteen PD patients and 18 matched control volunteers were instructed to look either toward (pro-saccade) or away from (anti-saccade) a peripheral stimulus as soon as it appeared (immediate, gap and overlap conditions) or after a variable delay; or, they made sequential saccades to remembered targets after a variable delay. We found that PD patients made more express saccades (correct saccades in the latency range of 90–140 ms) in the immediate pro-saccade task, more direction errors (automatic pro-saccades) in the immediate anti-saccade task, and were less able to inhibit saccades during the delay period in all delay tasks. PD patients also made more directional and end-point errors in the memory-guided sequential task. Their inability to plan eye movements to remembered target locations suggests that PD patients have a deficit in spatial working memory which, along with their deficit in automatic saccade suppression, is consistent with a disorder of the prefrontal-basal ganglia circuit. Impairment of this pathway may release the automatic saccade system from top-down inhibition and produce deficits in volitional saccade control. Parallel findings across various motor, cognitive and oculomotor tasks suggest a common mechanism underlying a general deficit in automatic response suppression.

Keywords: Basal ganglia; Anti-saccades; Frontal cortex; Pro-saccades; Gap effect; Express saccades

1. Introduction

The motor impairments of Parkinson's disease (PD), including muscle rigidity and slowness of movement (Lezak, 1995), result from degeneration of dopaminergic neurons in the substantia nigra pars compacta (Bergman & Deuschl, 2002; Leenders & Oertel, 2001). In addition to their slowed movements, individuals with PD are often impaired in their ability to suppress automatic behavioral responses (Henik, Singh, Beckley, & Rafal, 1993; Hayes, Davidson, Keele, & Rafal, 1998; Owen et al., 1993).

One set of simple behavioral tasks that may provide insight into the neural control of response suppression uses saccadic eye movements to investigate and quantify motor impairments in PD (Jones & De Jong, 1971; Shibasaki, Tsuji, & Kuroiwa, 1979; White, Saint-Cyr, Tomlinson, & Sharpe, 1983). Saccades can be measured easily and precisely; and, there is considerable understanding of the neural circuitry controlling the planning and execution of saccadic eye movements (Leigh & Zee, 1999; Munoz, Dorris, Paré, & Everling, 2000; Scudder, Kaneko, & Fuchs, 2002; Wurtz & Goldberg, 1989). Two types of responses are of interest for this study: visually triggered and volitionally guided saccades. Visually triggered saccades (sometimes called reflexive or automatic saccades) are inititated by the sudden appearance of a visual

Abbreviations: CV, coefficient of variation; DLPFC, dorsolateral prefrontal cortex; FEF, frontal eye fields; FP, fixation point; LED, light-emitting diode; MPTP, methyl phenyl tetrahydropyridine; PD, Parkinson's disease; REX, real-time data-acquisition system; SRT, saccadic reaction time

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stimulus and are mediated by the superior colliculus, with important inputs from the visual and posterior parietal cortices (Guitton, Buchtel, & Douglas, 1985; Hanes & Wurtz, 2001; Schiller, Sandell, & Maunsell, 1987). Volitionally guided saccades, generated by internal goals, sometimes in the absence of any overt triggering stimulus, rely upon circuitry that includes higher brain centers such as the frontal cortex and the basal ganglia (Dias & Segraves, 1999; Gaymard, Ploner, Rivaud, Vermersch, & Pierrot-Deseilligny, 1998; Hikosaka & Wurtz, 1989; Hikosaka, Takikawa, & Kawagoe, 2000). Volitionally guided saccades can be elicited by asking participants to look from a central point to the direction opposite the eccentric stimulus (the anti-saccade task; Munoz & Everling, 2004). For success in the anti-saccade task, participants must first inhibit a visually guided saccade towards the eccentric stimulus and instead prepare a volitional saccade to an area of the visual field without visual stimuli.

The study of saccadic inhibition provides a powerful, yet simple evaluation of control over volitional and automatic-reflexive processes (Everling & Fischer, 1998; Leigh, Newman, Folstein, Lasker, & Jensen, 1983; LeVasseur, Flanagan, Riopelle, & Munoz, 2001; McDowell, Brenner, Myles-Worsley, Coon, Byerley, Clementz, 2001; Munoz & Everling, 2004; Munoz, Armstrong, Hampton, & Moore, 2003; Ross, Harris, Olincy, & Radant, 2000). The aim of this study is to use pro- and anti-saccade tasks with immediate and delayed responses to quantify the control of automatic and volitional responses in individuals with PD. In addition, our battery of oculomotor tasks included a delayed memory-guided sequential task as a test of spatial working memory. The delayed memory-guided sequential task requires participants to suppress any eye movements during the delay period while remembering the spatial location of three targets that are flashed briefly, and then to plan the direction of movement before initiating any saccades. We measured the ability of PD patients to use spatial working memory correctly to plan eye movements to the remembered locations of the sequential targets.

2. Methods

2.1. Participants

All experimental procedures were reviewed and approved by the Queen's University Human Research Ethics Board. Eighteen mild to moderate PD patients (Hoehn–Yahr stages I–III; Hoehn & Yahr, 1967) were compared with 18 age-matched normal controls. The PD participants met clinical criteria for diagnosis and were referred by a neurologist (G.P. or R.J.R.). The PD group (11 of 18 were men) had a mean age of 67 years (range: 38–81 years). All PD patients were medicated and were not asked to interrupt their medication on the days of recording. Twelve patients were receiving dopamine precursor treatment (carbidopa/levodopa), nine were taking dopamine agonists (ropinirole, bromocriptine, pergolide, domperidone, or pramipexole), six were taking amantadine, four were taking a monoamine oxidase inhibitor (selegeline), and two were on anticholinergic medication (ethopropazine or trihexyphenidyl). All control participants (5 of 18 were men; mean age 65.7 years, ranging from 35 to 83 years) had no known neurological, psychiatric, or visual disorders. Participants wore corrective lenses if needed throughout the experiments. Participants were informed of the nature of the study and provided written consent to participate in the study in accordance with the Declaration of Helsinki.

2.2. Experimental paradigms

Participants were run in three separate experimental sessions. In the first session, participants performed one block of the *immediate* pro- and two blocks of the *immediate* anti-saccade task. Each block consisted of 120 trials. In a second session, participants performed the *delayed pro-/anti-saccade* task in three blocks (160 trials each). Each block contained randomly interleaved pro- and anti-saccade trials. In a third session, they performed two blocks (96 trials each) of the *delayed memory-guided sequential* task. Participants were given breaks between blocks of trials. Two PD patients did not complete the *delayed pro-/anti-saccade* task.

2.2.1. Immediate and delayed pro- and anti-saccade tasks

In the *immediate* and *delayed* pro-/anti-saccade tasks (Fig. 1), participants were seated in complete darkness facing the center of a translucent screen located 100 cm away. A red light-emitting diode (LED; 2.0 cd/m^2) was back-projected onto the center of the screen and served as a central fixation point (FP). The delayed task also used a green LED (2.0 cd/m^2) as a central FP that alternated randomly with the central red FP (see below). Red target LEDs (5.0 cd/m^2) were positioned 20° to the right and left of the central FP. The screen was diffusely illuminated between trials to decrease dark adaptation.

In the *immediate* pro-saccade task (Fig. 1A), participants were instructed to look to an eccentric target as soon as it appeared. Each trial began with a 250 ms period of complete darkness. The FP then appeared and after 1000 ms, one of two events took place. In the gap condition (Fig. 1C), the FP disappeared and, following a gap interval of 200 ms of darkness, the eccentric target appeared. During the overlap condition (Fig. 1D) the FP remained visible when the eccentric target appeared and throughout the remainder of the trial. Participants were instructed to look to the eccentric target as soon as it appeared. The target appeared randomly either 20° to the left or right and remained visible for 1000 ms, after which all LEDs disappeared and the background illumination reappeared signifying the completion of the trial. Target location (left or right) and fixation condition (gap or overlap) were randomly interleaved throughout each block of trials.