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# Initiation and inhibitory control of saccades with the progression of Parkinson's disease – Changes in three major drives converging on the superior colliculus

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ABSTRACT

The cardinal pathophysiology of Parkinson's disease (PD) is considered to be the increase in the activities of basal ganglia (BG) output nuclei, which excessively inhibits the thalamus and superior colliculus (SC) and causes preferential impairment of internal over external movements. Here we recorded saccade performance in 66 patients with PD and 87 age-matched controls, and studied how the abnormality changed with disease progression. PD patients were impaired not only in memory guided saccades, but also in visually guided saccades, beginning in the relatively early stages of the disease. On the other hand, they were impaired in suppressing reflexive saccades (saccades to cue). All these changes deteriorated with disease progression. The frequency of reflexive saccades showed a negative correlation with the latency of visually guided saccades and Unified Parkinson's Disease Rating Scale motor subscores reflecting dopaminergic function. We suggest that three major drives converging on SC determine the saccade abnormalities in PD. The impairment in visually and memory guided saccades may be caused by the excessive inhibition of the SC due to the increased BG output and the decreased activity of the frontal cortex-BG circuit. The impaired suppression of reflexive saccades may be explained if the excessive inhibition of SC is "leaky." Changes in saccade parameters suggest that frontal cortex-BG circuit activity decreases with disease progression, whereas SC inhibition stays relatively mild in comparison throughout the course of the disease. Finally, SC disinhibition due to leaky suppression may represent functional compensation from neural structures outside BG, leading to hyper-reflexivity of saccades and milder clinical symptoms.



## 1. Introduction

Although most of the anatomical connections and physiology of the basal ganglia (BG) within the oculomotor network have been studied in primates (Hikosaka & Wurtz, 1989; Kato et al., 1995; Kori et al., 1995), a similar oculomotor system organization has been suggested in humans by means of lesion (see Pierrot-Deseilligny, Milea, & Muri, 2004 for review) and neuroimaging studies (Brown et al., 2004; O'Driscoll et al., 1995; Sweeney et al., 1996). Outputs from BG reach the superior colliculus (SC) via the substantia nigra pars reticulata (SNr), where the SC serves as the common terminal for controlling visually and memory guided saccades, with converging commands arriving through the BG–SC pathway and cortex-SC pathways (Hikosaka & Wurtz, 1989). Since eye movement reflects the output of BG relatively directly, saccade recordings can provide insights into the pathophysiology underlying neurological disorders at the systems level, especially for BG disorders such as Parkinson's disease (PD) (Hikosaka & Wurtz, 1989). The SC is spared until the later stages of the disease, even when other neural structures, including the cerebral cortex, become affected (see Jellinger, 2001 for review). Cortical mechanisms could also explain the predominant impairment of voluntary saccades, such as functional changes in the frontal eye field and prefrontal cortices, especially in the later stages of the disease. We thus considered it important to examine the pathophysiology of PD using saccade performance as an indicator of BG function.

Although a number of human and primate studies have been conducted in this area, some aspects of the pathophysiology of PD remain unclear. The diagram presented by Alexander and Crutcher (1990) provides relatively clear explanations for Parkin-

*Abbreviations:* PD, Parkinson's disease; BG, Basal ganglia; SC, superior colliculus; VGS, visually guided saccade; MGS, memory guided saccade; SNr, substantia nigra pars reticulata; GPi, globus pallidus interna; GABA, gamma aminobutyric acid; GAP, gap saccade; RT, reaction time.

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**Table 1**
Patient characteristics.

| Subject group | Subject | Male | Female | Age (yr) | Onset age (yr) | Duration (yrs) | UPDRS motor score | Dopa equivalent dose (mg) | RT (ms) |
|---|---|---|---|---|---|---|---|---|---|
| Normal | 89 | 42 | 47 | 65.6 ± 4.3 | – | – | – | – | 417.6 ± 123.7 |
| H–Y stage 1 | 11 | 9 | 2 | 61.4 ± 10.9 | 58.0 ± 13.0 | 4.2 ± 3.5 | 12.1 ± 4.0 | 152.6 ± 194.2 | 429.3 ± 97.7 |
| H–Y stage 2 | 19 | 10 | 9 | 67.8 ± 9.8 | 62.3 ± 12.2 | 5.5 ± 3.8 | 21.4 ± 6.7 | 233.7 ± 203.6 | 573.4 ± 151.0 |
| H–Y stage 3 | 29 | 14 | 15 | 66.5 ± 9.7 | 59.6 ± 12.7 | 6.8 ± 5.2 | 31.0 ± 7.0 | 259.1 ± 229.2 | 642.6 ± 215.2 |
| H–Y stage 4 | 7 | 3 | 4 | 72.0 ± 12.0 | 60.2 ± 18.7 | 11.8 ± 7.3 | 45.1 ± 6.3 | 439.0 ± 184.7 | 783.1 ± 168.9 |

sonian symptoms. In PD, GABAergic inhibitory projection neurons of the BG output nuclei, the globus pallidus interna (GPi), and SNr exhibit overactive tonic firing rates and produce excessive suppression of the thalamus and the SC (Albin, Young, & Penney, 1995). This may prevent the thalamus from producing quick movements of appropriate size, resulting in bradykinesia/akinesia. As for oculomotor control, the SC is excessively inhibited by the overactive SNr and all types of saccades are thus suppressed. Indeed, saccades are hypometric and require a multistep sequence to reach the target in PD. Although highly simplified in some respects, the general framework of this classical model provides a good starting point and conceptual guide to understand the pathophysiology of PD.

Excessive SC inhibition, however, does not explain all aspects of saccade abnormalities in PD. Most studies have found marked impairment of memory guided saccades (MGS), saccades made to remembered target locations in the absence of a visual target, whereas visually guided saccades, which are made to targets appearing at unpredictable locations, are relatively spared (e.g., Briand, Strallow, Hening, Poizner, & Sereno, 1999; Bronstein & Kennard, 1985; Vidailhet et al., 1994). The involvement of the BG in PD appears to provide a good explanation for this dissociation, since different neural structures subserve both types of saccades. For the visually guided saccades, the parietal eye field, including the posterior parietal cortex, mainly integrates visuospatial information to generate a motor signal that is sent to the SC via the parietal lobe-SC pathway (Gaymard, Lynch, Ploner, Condy, & Rivaud-Péchoux, 2003). In contrast, the processing for MGS, a voluntary saccade, mainly takes place in the frontal lobe, where the motor signal is emitted directly or via the BG to the SC (the direct pathway of the BG circuit). A phasic reduction from the high resting rates of the SNr temporarily releases the saccade cells in the recipient SC, resulting in the generation of voluntary saccades (Hikosaka & Wurtz, 1985a, 1985b, 1989).

However, it is not only the voluntary saccades such as MGS that are affected but also visually guided saccades. Other saccade abnormalities in PD do not fit in with the aforementioned views. Along with the impairment of memory guided saccades, some studies have found a mild but definite abnormality of visually guided saccades (Rascol et al., 1989; Shibasaki, Tsuji, & Kuroiwa, 1979). PD patients also have difficulty in suppressing unwanted saccades to the novel appearance of visual targets (Chan, Armstrong, Pari, Riopelle, & Munoz, 2005; Joti, Kulashekhar, Behari, & Murthy, 2007; Kitagawa, Fukushima, & Tashiro, 1994; van Koningsbruggen, Pender, Machado, & Rafal, 2009; van Stockum, MacAskill, Anderson, & Dalrymple-Alford, 2008), which is also an important function of the BG.

The drive to suppress the excitability of the SC and impair saccade initiation and that leading to its "hyper-reflexivity" are in apparent contradiction if they were to converge in the SC. Excessive inhibition of SC would tend to prolong latencies of visually guided saccades. Conversely, if "hyper-reflexivity" predominates, we would expect that the latency of visually guided saccades would be shortened. Indeed, there is no agreement among many of the above studies as to whether the latency of visually guided saccades, including VGS and gap saccades (see below), is shortened or prolonged. A recent meta-analytic review across 47 studies (Chambers & Prescott, 2010) suggested that PD patients initiate saccades faster than controls at small target eccentricities, while they respond more slowly for large eccentricities. However, the target eccentricity effect has not been formally ascertained in a single study, and how this trend happens and also how it relates to the pathophysiology of PD remains entirely unknown.

Altogether, a comprehensive explanation that can integrate all aspects of saccade abnormalities is still lacking. Although anatomical studies have shown that the FEF (Stanton, Deng, Goldberg, & McMullen, 1989) and SEF (Shook, Schlag-Rey, & Schlag, 1990) innervate the brainstem saccade generator directly, direct frontoreticular projections from frontal eye field do not appear to be sufficient to evoke saccades (Hanes & Wurtz, 2001) and thus the majority of cortical saccade-related brain areas influence saccade generation by projections to SC neurons, which then project to the brainstem saccade generators (Johnston & Everling, 2008). The present study aimed to clarify the pathophysiology of PD through saccades from the perspective of the SC. For this purpose, unlike previous studies, we considered it important to study saccades toward targets of different eccentricities (5–30°), since saccades of large and small amplitudes may be generated by a different mechanism and the extent to which inhibition is involved may also differ (van Donkelaar, Saavedra, & Woollacott, 2007). We studied saccade parameters in PD patients at various stages to investigate how the initiation and inhibitory control of saccades varied with the advance of the disease. To measure the inhibitory control of saccades, we studied the frequency of saccades to cue, that is, inadvertent saccades made to a visual cue presented during an MGS task, instead of directional errors in the antisaccade task. Insights into the pathophysiology of PD would support the usefulness of saccadic parameters as a biomarker for gauging the progression of the disease (Blekher et al., 2009) and would also help in optimizing the treatment. This study has been previously presented in abstract form (Terao et al., 2007).

## 2. Methods

### 2.1. Subjects

Sixty-six PD patients (36 men, 30 women, age: 66.7rf ± 10.6, Hoehn and Yahr [H–Y] stages 1–4.5 (on medication), disease duration: 6.5 ± 5.3, Table 1) were studied, with a mean Unified Parkinson's Disease Rating Scale (UPDRS) motor score (on medication) of 26.8 ± 11.3 (range: 7–56.5). Patients with mini-mental state examination scores of less than 25 and those with psychiatric and affective disorders were excluded. We also collected control data from 89 age-matched normal subjects (42 men, 47 women, age: 65.6 ± 4.3).

Experiments were conducted as part of clinical assessment according to the guidelines of the local ethical committee after obtaining informed consent. Both for ethical and practical reasons, patients had to continue taking their regular doses of medication. This was because many of the studied patients were outpatients who had to commute to visit our hospital to take the tests. In addition, some advanced patients could not do without dopaminergic medication to carry on with their daily life, and were not able to properly perform the task trials, which were all started by a button press and terminated by a button release (see below).

PD medications can influence parameters of saccadic eye movement (Michell et al., 2006). To cope with this problem, we studied the saccade performance in 10 denovo PD patients in preliminary experiments, who took their first dose of L-dopa (100–200 mg). We followed up the saccade performance of VGS and MGS for 4 h (Yugeta, Terao, Fukuda, & Ugawa, 2008). There was a small effect both on latency and amplitude of visually and memory guided saccades, which effect was maximal at around 1–2 h but faded away by 3 h of intake. Thus, the subjects' performance was measured 4 h after the final intake of L-dopa in the morning.