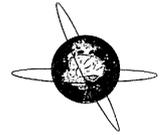


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Review

New perspectives on the pathophysiology of Parkinson's disease as assessed by saccade performance: A clinical review



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HIGHLIGHTS

- We review the pathophysiology of basal ganglia (BG) dysfunction in Parkinson's disease (PD) based on saccade performance.
- Saccade abnormalities in PD may be caused by the excessive inhibition of the superior colliculus (SC) due to the increased BG output and decreased activity of the frontal cortex-BG circuit, as well as impaired suppression of reflexive saccades that may be explained by the "leaky" suppression of the SC.
- Treatment of PD, such as L-dopa therapy and deep brain stimulation, works by normalizing these abnormal BG functions, but in different ways.

ABSTRACT

We reviewed basal ganglia (BG) dysfunction in Parkinson's disease (PD) based on recent findings on saccade performance. Hypometria in all saccade paradigms and impaired initiation of internally triggered saccades such as memory guided saccades (MGS) are reported, whereas visually guided saccades (VGS) are relatively spared, although they are also mildly affected. The ability to inhibit unwanted saccades is also impaired. We propose that three major drives converges on SC to determine the saccade abnormalities. The impairment in VGS may be caused by the excessive inhibition of SC due to the increased BG output, whereas for MGS, decreased activity of the frontal cortex-BG circuit may also be involved. The impaired suppression of unwanted saccades may result from the "leaky" inhibition of SC. When PD patients inspect pictures, they end up exploring a smaller area of them with smaller saccades compared to normal subjects. Levodopa slightly prolongs VGS latency and shortens MGS latency, by altering the balance between the direct and indirect pathways of the BG circuit. In contrast, deep brain stimulation of the subthalamic nucleus improves saccade hypometria in both VGS and MGS, presumably by acting relatively directly on the SC-substantia nigra pars reticulata pathway to remove the excessive SC inhibition.

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1. Introduction

Most of the anatomical connections and physiology of the basal ganglia (BG) within the oculomotor network have been extensively studied in primates (Hikosaka and Wurtz, 1989; Hikosaka et al., 2000), and the existence of a similar oculomotor system organization in humans is supported by means of lesion (see Pierrot-Deseilligny et al., 2004 for review) and neuroimaging studies (O'Driscoll et al., 1995; Sweeney et al., 1996; Brown et al., 2004). These studies provide a firm basis for the clinical application of eye movement examination.

Based on the findings of primate neurophysiology, which were already abundant by the 1980s, clinical studies of eye movement have emerged as a promising non-invasive tool to investigate the underlying brain pathophysiology in various neurological disorders and to help diagnose the patients suffering from such disorders. Saccade recordings have helped to provide a non-invasive measure in the clinical setting to probe the function of the neural system implicated in oculomotor control, especially the BG, and a number of saccade studies have been conducted to clarify characteristic patterns of saccade abnormalities in various neurological disorders (DeJong and Jones, 1971; Teräväinen and Calne, 1980a, b; White et al., 1983; Vidailhet et al., 1994; Briand et al., 1999; Kimmig et al., 2002; Sweeney et al., 1996; Blekher et al., 2009), e.g., saccades of slow velocity in patients with progressive supranuclear palsy (Pierrot-Deseilligny et al., 1989; Vidailhet et al., 1994; Rottach et al., 1996; Rivaud-Péchoux et al., 2000b; Terao et al., 2013). Successful as they were in differentiating neurological disorders through oculomotor measures, many studies served to confirm what had been already found in primate studies rather than being directed at providing a comprehensive insight into the underlying pathophysiology of neurological patients, while other studies address movement disorders such as progressive supranuclear palsy which do not have an appropriate animal model. Even the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model fails to account for all features of PD such as progressive neurodegeneration. Therefore, while miscellaneous findings of saccadic dysfunction in neurological disorders have been reported, both clinical findings of saccade performance and insights gained from basic primate studies should complement each other to arrive at a comprehensive explanation capable of integrating all aspects of saccade abnormalities. For example, although hypometria and prolonged latencies in various oculomotor paradigms are frequently observed both in PD patients and in those with cerebellar ataxia, what difference is there in the underlying pathophysiology between the two categories of neurological disorders? It has long been known that patients with cerebellar ataxia under- or overshoot the target, then make refixation saccades to the target (Flaherty and Rost, 2007). On the other hand, patients with extrapyramidal bradykinesia make hypometric saccades, regardless of the task. Obviously, the hypometria in both these disorders cannot share the same origin.

Other types of eye movements are also affected in PD. PD patients even at early stages may show impaired smooth pursuit with reduced gain, both horizontally and vertically, due partly to hypometric catch-up saccades, as well as impaired convergence and

combined eye-head tracking (White et al., 1983, 1988; Waterston et al., 1996; Bares et al., 2003; Leigh and Zee, 2006). Interestingly, despite the reduced gain of smooth pursuit, the phase relationship between the eyes and target movement is relatively spared, which implies normal predictive tracking strategies in PD (Bronstein and Kennard, 1985). In this review, we focus on the abnormalities of saccades.

Although the Braak hypothesis (Braak et al., 2003) states that neurodegeneration in PD initially occurs in the brainstem structures including the dorsal motor nucleus of the glossopharyngeal and vagal nerves and anterior olfactory nucleus, within the oculomotor system, the neural degeneration may be considered to be relatively restricted to the striatonigral system at least at its earliest stage (Jellinger, 2001). Thus, PD provides an optimal situation in which we can study how BG dysfunction affects saccade parameters. Recently, however, it is becoming clear that the traditional BG network model for saccade control is too limited to account for many of the behavioral changes observed in this disorder (Watanabe and Munoz, 2011). Herein, we reviewed how saccade studies have arrived at new perspectives on the BG pathophysiology in this disease.

2. Two categories of saccade paradigms used for clinical studies: externally and internally guided saccades

Volitional saccades are categorized into two main classes, those made in response to a visual cue (externally or visually guided saccades in the "broad" sense), which are considered rather "reflexive" in nature, and those made in the absence of such a cue and are therefore considered to be more "voluntary" (internally guided saccades). When we study saccades in the laboratory setting, oculomotor paradigms that correspond to these two types are used: the visually guided (VGS) and memory guided saccade (MGS) tasks (see below) are among the most commonly employed behavioral paradigms.

In the VGS task (in the narrow sense, Fig. 1A), a fixation point is typically turned on in the middle of the dome and subjects are instructed to fixate on it as quickly as possible. It is then turned off after a period, and immediately thereafter, a target point is turned on at a random location at various target eccentricities, typically 5–30 degrees, horizontally to the left or right of the original fixation point. The subjects fixate on the new target as quickly as possible. A variant of VGS is the gap saccade (GS) paradigm, which is identical to the VGS task except that the target spot is turned on 200 ms after the fixation point is extinguished.

The MGS task (Fig. 1B), originally developed by Hikosaka and Wurtz (1983), is a task in which the subjects make a saccade according to their memory of the target location (i.e., in the absence of a visual signal). While the subject fixates on the central spot, a peripheral stimulus ("cue") appears for a brief period (e.g., 50 ms). The subjects are to maintain fixation until the central spot is turned off, at which time they are to make a saccade to the spatial location where the cue appeared. Saccades unintentionally made to the cue during the delay period are called "saccades to cue." Therefore, this task is suitable not only for assessing the

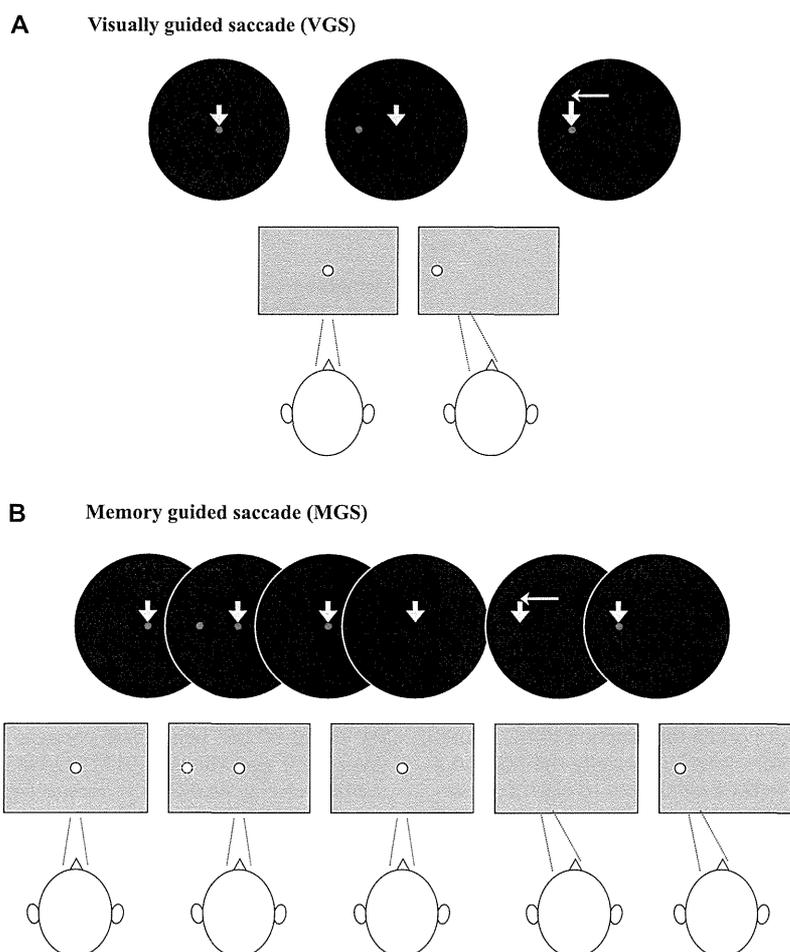


Fig. 1. Oculomotor tasks used for clinical saccade studies (A: VGS, B: MGS). In VGS (A), first, a central spot of light which subjects were required to fixate was turned on. After a random period of time (1.2–2.0 s), the fixation spot was extinguished, and a target stimulus simultaneously appeared randomly to the left or right of it. The subjects were to foveate the target as quickly as possible. In the MGS task (B), while the subject fixated the central spot, a peripheral stimulus (“cue”) appeared for a brief period of 50 ms. The subjects were required to maintain visual fixation until the fixation point was turned off (delay period), when the subjects had to make a saccade based on their memory to the spatial location where the cue had appeared.

ability to generate voluntary saccades but also for investigating the inhibitory control of saccades; when the latter ability is impaired, there will be an increase in the frequency of saccades to cue.

The antisaccade task (AS) is a task in which the subject, after presentation of a peripheral target, looks away to its mirror position. This requires them to inhibit a reflexive saccade toward the target (termed a *prosaccade*), and instead generate a voluntary saccade toward a mirror position without a visual stimulus. Thus, this task is considered to fall also into the “voluntary” category. For this task, the frequency of *prosaccades* is considered to reflect the subject’s ability to suppress unwanted saccades.

3. Superior colliculus as a “bottleneck” of neural structures responsible for the generation of volitional saccades

Generation of saccades, both visually guided and voluntary, are controlled differently by separate parallel descending pathways involving the cerebral cortex (the frontal and parietal areas), BG, and the superior colliculus (SC), and the brainstem saccade generator. Although anatomically, frontal cortical regions such as the frontal eye field (Stanton et al., 1989) and supplementary eye field (Shook et al., 1990) innervate the brainstem saccade generator directly, direct projections from these areas are not considered

functionally sufficient to evoke accurate saccades when corresponding sites in the SC are inactivated (Hanes and Wurtz, 2001; Fig. 2, left). Therefore, the SC may constitute the “final common pathway” for purposive saccades, with converging commands arriving through the BG-SC and cortex-SC pathways, including projections both from the frontal and parietal cortices (Hikosaka et al., 2000). The BG process signals from the frontal oculomotor areas which funnel to the SC; outputs from the BG reach the SC via the substantia nigra pars reticulata (SNr). In the clinical setting, since eye movement reflects the output of the BG relatively directly, saccade recordings can provide useful insights into the pathophysiology underlying neurological disorders at the systems level, especially for BG disorders such as PD (Hikosaka et al., 2000; Terao et al., 2011a).

The processing involved in 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 and Wurtz, 1983, 1985b). Therefore, the performance of MGS reflects the functioning of the direct pathway of the BG circuit implemented through this mechanism of “double inhibition” (Hikosaka et al., 2000).

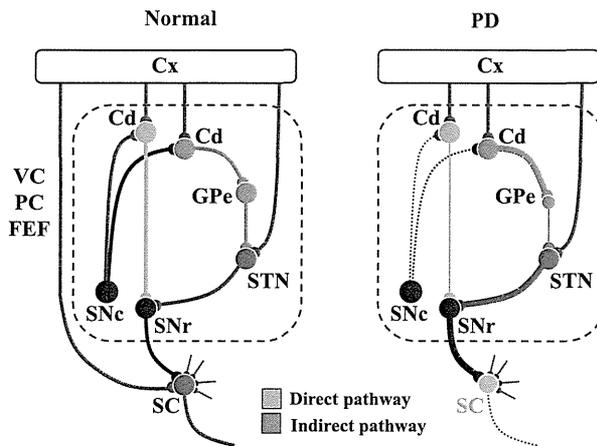


Fig. 2. Schematic diagram showing the neural structures depicting the pathophysiology underlying saccade abnormalities in PD. Left figure: Schematic diagram depicting the neural structures involved in the control of saccades in a normal subject. Red lines indicate excitatory connections and black, blue, and purple lines indicate inhibitory connections. The dotted area designates the BG circuit. The blue curves denote the direct pathway and purple curves the indirect pathway (also see panel linked to the bottom of the figure). The pathways involved in the volitional control of saccades all converge onto the SC. Note that most of the inputs converging onto the SC are excitatory, while the only inhibitory input is from the basal ganglia (in the case of saccades, SNr). Some recent studies suggest the existence of direct projections from the prefrontal cortex to the brainstem saccade generator that play an important role in saccade inhibition, but these are not included in this figure. On the other hand, ascending inputs from the SNc to the caudate nucleus change the balance between the activity of the direct and indirect pathways of the BG also decreases. These changes may explain why both VGS and MGS are affected in PD, and also why the degree of involvement is much stronger for the latter. Cd: caudate, Cx: the cerebral cortex, SC: superior colliculus, SNc: substantia nigra pars compacta, SNr: substantia nigra pars reticulata, GPe: external segment of the globus pallidus.

For VGS and GS, on the other hand, 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 et al., 2003b). Thus, the processing involved in VGS is considered largely to bypass the BG circuit.

Note that while most of the inputs reaching the SC are excitatory, the main inhibitory pathway impinging on the SC is from the BG, excluding inhibitory circuits intrinsic in the brainstem and within the SC (see below). Therefore, unlike limb movements, the control of saccades primarily depends on inhibition (or release of inhibition, “disinhibition”). For example, the initiation of MGS is controlled by the tonic inhibition of the SC, which is released only when one wants to make a saccade.

The majority of cortical saccade-related brain areas influence saccade generation by projections to SC neurons both for reflexive and voluntary saccades, by way of the SC’s well-organized motor map representing saccades of different sizes and its well-characterized neuronal elements (Munoz and Fecteau, 2002), but they also play an important role in the inhibitory control of saccades. Above the brainstem level, the BG-SC pathway is believed to be the only inhibitory pathway. Recently, however, the frontal cortical regions are also thought to exert direct inhibition of the brainstem saccade generator (Guitton et al., 1985; Gaymard et al., 2003a; Condy et al., 2004, 2007; Fukushima et al., 1994; Pierrot-Deseilligny, 1991; Pierrot-Deseilligny et al., 2004; Hodgson

et al., 2007). The dynamic interactions between the excitatory and inhibitory inputs arriving into the SC determine the target-related activity in the SC, which strongly correlates with the saccade reaction time (Dorris and Munoz, 1998; Munoz and Fecteau, 2002; Fecteau et al., 2004). Therefore, in the following, we looked at these findings from the perspective of the SC.

4. Prominent features of saccade abnormality in Parkinson’s disease

Saccade abnormalities in PD patients have been addressed by a number of studies. Among them, the most consistently noted saccade abnormality in PD patients is that involving markedly hypometric saccades in all types of oculomotor tasks, including VGS and MGS (Fig. 3). Because of these hypometric saccades, PD patients often need to utilize a multi-step sequence to reach the target (DeJong and Jones, 1971; Jones and DeJong, 1971). For voluntary saccades such as MGS, the hypometria is so pronounced that it may be accurately called a fragmentation of gaze shifts (target is reached by several hypometric saccades) (Kimmig et al., 2002). This kind of multiple step pattern is very remarkable in PD and some authors even consider it to be a biomarker in PD (Blekher et al., 2009).

Another prominent saccade abnormality in PD patients is that they have difficulty in initiating voluntary saccades such as MGS (Crawford et al., 1989; Nakamura et al., 1994; Vermersch et al., 1994) and AS (Lueck et al., 1990; Kitagawa et al., 1994; Briand et al., 1999; Chan et al., 2005), with decreased accuracy (Bronstein and Kennard, 1985; Ventre et al., 1992; Hikosaka et al., 2000). In contrast, externally triggered saccades to visual targets, whose generation largely bypasses the BG, such as VGS, are relatively spared (White et al., 1983; Rascol et al., 1989; Vidailhet et al., 1994; Briand et al., 2001). The preferential impairment of voluntary saccades such as MGS has been explained by the fact that the BG are more involved in voluntary saccades such as MGS (see previous section; Kori et al., 1995; Fukushima et al., 1994; Briand et al., 1999; Pierrot-Deseilligny et al., 2004). Similarly, for the AS task, another type of voluntary saccade, the latency is delayed, accuracy is reduced, and subjects make increased error saccades toward the target (Kitagawa et al., 1994; Briand et al., 1999).

The abnormality of saccade performance in PD is consistent with the prevailing view on the pathophysiology of PD: that the patients are more impaired in making internally guided movements, which are performed on the basis of an internal representation of the movement pattern, than in making externally guided movements, which are relatively preserved (e.g., VGS; see Bernardelli et al., 2001 for review). This apparent dichotomy has also been invoked to explain the treatment effects of dopaminergic drugs and deep brain stimulation (DBS), which were widely believed to improve internally but not externally guided saccades. This simple dichotomy, however, has recently come to be challenged, as we will now discuss.

5. Pathophysiology of PD viewed from the perspective of the superior colliculus

Some saccade abnormalities in PD do not neatly fit the aforementioned dichotomized view of externally versus internally generated saccades. For example, a mild but definite abnormality of reflexive saccades has been demonstrated, including VGS, which was previously thought to be relatively spared (Shibasaki et al., 1979; Rascol et al., 1989; Chambers and Prescott, 2010). Terao et al. (2011a) recorded saccade performance in 66 patients with PD at various stages of the disease, and found that the delay in VGS latency was actually quite a consistent finding. This delay also

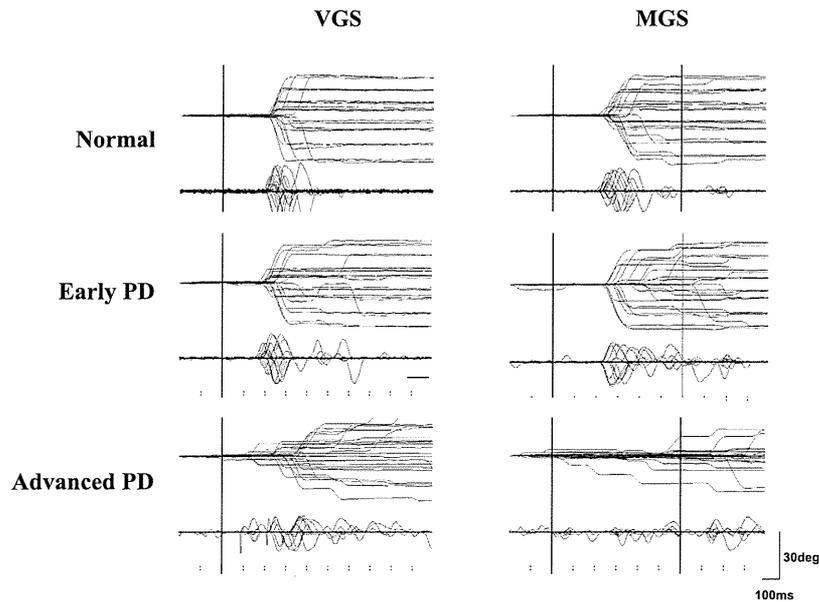


Fig. 3. Traces of VGS and MGS. Traces of VGS and MGS in a normal subject (top row) and in a single patient with early and advanced PD (middle and bottom rows). Horizontal electro-oculographic (EOG) recordings were made using two Ag–AgCl gel electrodes of 1.0 cm diameter placed at the bilateral outer canthi with an adhesive margin. Vertical EOG recordings were made using the same electrodes placed above and below the right eye. The signals were fed to a DC amplifier that was low-pass filtered at 20 Hz and then digitized (500 Hz). Twenty to 30 trials of eye movements (upper traces) and velocity curves (lower traces) are superimposed and are time-locked to the presentation of the target (VGS) or to the offset of the central fixation point (MGS). The abscissa is the time axis and the ordinate gives the angle. Note the hypometria both in the VGS and MGS tasks, especially for the latter at advanced disease stages. Initiation of MGS is impaired at advanced stages of PD. Reproduced with permission from Terao et al. (2011a).

varied with disease progression (Terao et al., 2011a) and with cognitive impairment (MacAskill et al., 2012).

Therefore, not only voluntary saccades such as MGS but also externally triggered saccades such as VGS are affected in PD, though to a milder degree. These findings are not consistent with the aforementioned externally over internally guided saccade dichotomy. It is thus necessary to revise the pathophysiological view of PD from the perspective of the SC, which comprises the bottleneck region for reflexive and voluntary guided saccades.

Although oversimplified in some respects, the classical model proposed by Alexander and Crutcher (1990) provides relatively clear explanations for many aspects of parkinsonian symptoms. Here dopamine deficiency leads to decreased activity of the direct pathway and increased activity of the inhibitory indirect pathway, especially of the subthalamic nucleus (Bergman et al., 1998), resulting in the increased activity of GABAergic inhibitory projection neurons of the BG output nuclei. The decreased activity of the direct pathway leads to the impaired initiation of voluntary saccades such as MGS, which have been shown to use this pathway for their initiation (see Hikosaka et al., 2000, for review). On the other hand, the internal segment of globus pallidus (GPi) and SNr exhibit overactive tonic firing rates and excessively suppress the thalamus and the SC which is downstream from it (Albin et al., 1995; Fig. 2, right). This may prevent the thalamus from producing quick movements of an appropriate scale, resulting in bradykinesia/akinesia. In terms of oculomotor control, it is thought that SC is excessively inhibited by the overactive SNr and that all types of saccades are thus suppressed. Indeed, electrical stimulation of the SNr, causing the inhibition of the SC, reduces the amplitude of both VGS and MGS in primates (Basso and Liu, 2007). Prolongation of VGS as well as the reduced velocity and amplitude for all types of saccades may thus be explained by the excessive SC inhibition via the BG (Machado and Rafal, 2004). Conversely, deep brain stimulation of the subthalamic nucleus (STN DBS), which is thought to reduce the level of SNr–SC inhibition, improved VGS and MGS in PD patients (see below; Yugeta et al., 2010). In the

Yugeta et al. study, hypometria of VGS as well as MGS were improved, supporting the notion that SC serves as the “bottleneck” region for all types of volitional saccades.

6. The pathophysiological basis of hypometric saccades and gaze shift fragmentation in PD

While the excessive suppression of the SC provides a good explanation for the hypometria observed in all types of saccades in PD, it does not sufficiently account for the dissociation in the degree of hypometria or gaze shift fragmentation between externally and internally triggered saccades, with the latter more significantly affected than the former. Kimmig et al. (2002) suggested that such “gaze shift segmentation” occurs because in PD the pre-oculomotor drive through the BG to the SC becomes abnormally weak and/or because the SC is under excessively strong inhibition. We suggest that both of these factors are at work in the hypometria of saccades in PD; the hypometric saccades in PD patients may be caused by two different mechanisms for VGS and MGS. The initiation of sensory driven saccade such as VGS would arise in the posterior parietal cortex that is directly connected to the SC (Pierrot-Deseilligny et al., 2004). Therefore, the abnormality of VGS may be explained mainly by the excessive inhibition of the “bottleneck” SC. In contrast, along with this excessive inhibition, MGS engage two serial inhibitory projections mediated by the frontal cortex (FC) and the BG, finally reaching the SC, as Kimmig et al. (2002) have suggested, and should also reflect the reduced pre-oculomotor drive.

Terao et al. (2011a) looked at how the pre-oculomotor drive and SC inhibition changes with the progression of PD. The VGS amplitude initially became progressively reduced as the disease progressed, although to a much smaller degree than did the MGS amplitude. SC suppression as reflected in VGS may thus comprise only a portion of PD pathophysiology. Although VGS latency and amplitude tended to worsen with the stage of the disease,

especially from Hoehn–Yahr (H–Y) stage 1 to 2, after that it tended to stabilize.

At the same time that the VGS latency was slowing and the VGS amplitude was decreasing, the MGS latency progressively increased and MGS amplitude decreased while the MGS success rate declined with the advance of the disease. This suggests that the function of the FC–BG circuit, reflecting the function of the direct pathway of the BG circuit, deteriorated along with the progression of the disease. The success rate of MGS appears to reach a minimum level at H–Y stages 3 to 4 due to an exhausted dopaminergic state. Hypometria in MGS is more pronounced than in VGS, probably because MGS is affected by both the excessive inhibition of the SC and the deteriorated pre-oculomotor drive through the FC–BG circuit.

As an alternative possible explanation for the hypometric saccades in PD, changes in cerebellar function in the presence of BG dysfunction would merit discussion. However, whether this could be addressed directly through saccade recordings is elusive, since saccades in PD are hypometric for almost all types of oculomotor paradigms and hypermetric saccades typical of cerebellar disorders are seldom observed. Brain imaging studies in PD patients using a variety of motor tasks have found hyperactivation in the cerebellum, which is considered to reflect compensation for the BG dysfunction (Rascol et al., 1997; Wu and Hallett, 2005; Yu et al., 2007). On the other hand, resting tremor in PD is considered to arise from a pathological interaction between the BG and the cerebellothalamic circuit, in the presence of dopamine-depleted BG (Helmich et al., 2011). In addition, an interaction is observed in a motor timing task which is considered to involve both the cerebellum and BG (Bares et al., 2011). Husárová et al. (2011) applied a predictive motor timing task to early PD patients and normal controls, which required the subjects to postpone their actions until the right moment (such as in the MGS task) and to adapt their behavior from one trial to the next. PD patients were impaired both in postponing and adapting their motor action. Functional magnetic resonance imaging during the task performance suggested a general “hypoactivation” of both the BG and the cerebellum in early stage PD patients compared to healthy controls. Though differing as regards hypo- and hyperactive cerebellar function, these studies do suggest some interaction between the BG dysfunction and cerebellar function in PD.

Saccade adaptation tasks may be useful to address the interaction of BG dysfunction with the cerebellar function in PD, since saccade accuracy is maintained over time through adaptive ability mediated by the cerebellum. MacAskill and colleagues (2002) studied the performance of saccade adaptation task, both using the VGS and MGS, in PD patients and compared it with that of normal subjects. In this study, adaptation was induced by consistently but imperceptively displacing targets as saccades were made toward them, causing artificial saccadic inaccuracy. They hypothesized that adaptation of MGS would be impaired in PD, since BG dysfunction can disrupt the operation of the prefrontal cortex, while adaptation of VGS would be preserved. Compared to normal subjects, PD patients were less able to modify saccadic size appropriately for MGS (they showed excessive hypometria following the adaptation of MGS), but was normal in adapting the size of VGS. Although saccadic adaptation may involve structures other than the cerebellum, the saccade adaptive ability was generally spared in PD, indicating normal cerebellar function.

7. Saccade disinhibition in PD and its relationship to target eccentricity

Aside from the hypometric saccades in all oculomotor paradigms and the delayed initiation of voluntary saccades, the

inhibitory control of saccades is also impaired. PD patients also have difficulty in suppressing unwanted saccades to the novel appearance of visual targets (Joti et al., 2007; van Stockum et al., 2008; van Koningsbruggen et al., 2009), which is also an important function of the BG. For example, PD patients make more saccades to cue in the MGS task, which are saccades unintentionally made to the cue presented during the delay period (Fig. 4). In addition, PD patients experience difficulty in suppressing unwanted saccades of both a reflexive and voluntary nature (e.g., to inhibit saccades during the delay period of the delayed pro- and anti-saccade tasks), indicating a “hyper-reflexivity” of the saccades (Kitagawa et al., 1994; Chan et al., 2005).

The impairment of inhibitory control is difficult to explain within the context of excessive SC suppression, which would naturally result in inhibition of reflexive saccades (Machado and Rafal, 2004). Moreover, it should be noted that the drive to suppress the excitability of the SC and impair saccade initiation and that leading to its “hyper-reflexivity” would counteract one another if they were to converge in the SC.

The impairment of inhibitory control also poses a problem when explaining the changes in VGS latency in PD patients. Excessive inhibition of the SC would tend to prolong the latencies of VGS, as we have seen in the previous section. If “hyper-reflexivity” predominates, however, the latency of VGS would be shortened because of SC disinhibition. In fact, PD patients are known to be able to generate express saccades (very fast reflexive responses), with a latency of 80–120 ms (Biscaldi et al., 1996; Roll et al., 1996), and some studies have found that the generation of externally triggered saccades is usually found to be within the normal range or even faster in early PD patients than in normal subjects (Armstrong et al., 2002; Briand et al., 1999; Chan et al., 2005; Venre et al., 1992). Using prosaccade (“look towards”), delayed (“wait for cue”) and AS (“look away”) tasks, van Stockum et al. (2008) showed that PD patients made more express saccades in the prosaccade task with a gap (GS), more timing errors in the delayed response task, and more directional errors in the AS task than did the control group. These results indicate an enhancement of externally triggered saccades, in the direction of “hyper-reflexivity”, but in apparent contradiction with the prolonged latency of VGS as discussed in the previous section. Although all these studies point to the facilitation of visually guided “reflexive” saccades, there is no agreement among many of the above studies as to whether the latencies of externally triggered saccades, such as VGS and gap saccades, are shortened or prolonged. Terao et al. (2011a) have shown an increase in the frequency of saccades to cue, but have also demonstrated an increase in the latency of VGS, which at first sight is difficult to reconcile in the context of the “facilitation” and “suppression” of the SC.

These inconsistencies may arise in part from the fact that different studies use different target eccentricities for studying saccades; most of the studies to date used only one or two target eccentricities in the oculomotor paradigms to investigate saccade performance. A recent meta-analytic review of 47 studies (Chambers and Prescott, 2010) suggested that overall, PD patients, especially at early stages, initiate saccades faster than do controls at small target eccentricities, while they respond more slowly for large eccentricities. Using four different target eccentricities for studying saccades, Terao et al. (2011a) also showed that when early PD patients performed VGS, the histograms of latency distribution showed a prominent peak in the early range (110–150 ms) but only for small target eccentricities of 5–10 degrees, whose latency approached that of express saccades. The production of express saccades or short latency saccades at small target eccentricities was considered to be mainly due to an automatic increase in the excitability of SC saccade neurons after the fixation point offset (Biscaldi et al., 1996; Munoz et al., 2000), due to impaired

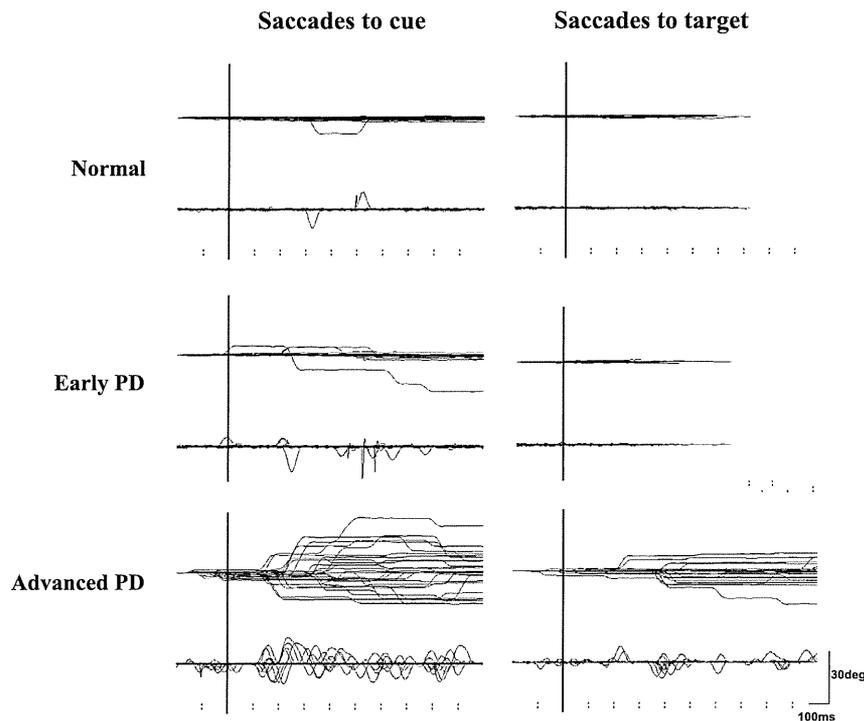


Fig. 4. Traces of saccades to cue and saccades to target. Inadvertent eye movements made during the delay period of MGS (saccades to cue) and during the hand reaction time (RT) task (saccades to target) in a normal subject (top row) and in a single patient with early and advanced PD (middle and bottom rows). See text for details of saccades to cue. In the hand RT task, the subjects held a microswitch button which was connected to the microcomputer and allowed them to initiate and terminate a trial by pressing and releasing the button with their thumb. A central spot of light comes on shortly after the subject presses a button, and it stays on throughout each trial. The subjects were instructed to fixate on it continuously. After a random period (2–6.5 s), another spot is illuminated at one of various eccentricities (5–30 degrees) and the subjects release the button as soon as possible while fixating on the central cross point. Inadvertent saccades made to the target are termed “saccades to target.” Note that in PD patients, both the frequencies of saccades to cue and those to target are higher than in normal subjects. The abscissa is the time axis and the ordinate gives the angle. Reproduced with permission from Terao et al. (2013).

inhibitory control of saccades. These early-latency saccades disappeared at advanced stages and the latency of saccades toward large target eccentricities became more prolonged than for normal subjects. These findings may suggest that saccades toward small eccentricities may especially show a tendency toward disinhibition.

Recent studies show that small and large amplitude saccades are generated by different mechanisms. van Donkelaar et al. (2007) demonstrated that when a peripheral object is foveated by a sequence of multiple saccades, the initial saccade in the sequence is initiated markedly faster than is a single accurate saccade to the same object, and they concluded that multiple saccades are generated in a more automatic manner than are single saccades. To explain this observation, they suggested that large amplitude saccades toward a visual target can become more fully planned when the cortically mediated inhibition is stronger and allows time for the programming to be completed, whereas small amplitude saccades can be more automatically produced (Reddi and Carpenter, 2000; Neggers et al., 2005; Carpenter, 2004).

Thus, it is expected that small amplitude saccades can be initiated with a very short latency unless they are under sufficient inhibition, whereas this may not be the case for large amplitude saccades. In normal subjects, it has been shown that it is more difficult to suppress reflexive saccades (“saccades to cue”) toward targets of 5-degree eccentricity than toward targets of 30-degree eccentricity during the delay period in the MGS task (e.g., Terao et al., 2011a). Moreover, in MGS trials, the delay period (600–1000 ms) allows for enough time to program saccades both of smaller and large amplitudes. Here smaller saccades are even slightly slower to initiate than are larger saccades (Hikosaka et al., 1993, 1995). This implies a stronger inhibition exerted on

smaller rather than on larger saccades until they can be finally released. The same is true for voluntary saccades such as AS for which the latency is longer than externally triggered saccades such as VGS and GS (Amador et al., 1998; Terao et al., 2011b).

If BG function is compromised and sufficient inhibition is lacking, unwanted smaller amplitude saccades can occur with a very short latency. Indeed, in early PD patients, only saccades made toward small target eccentricities (5–10 degrees) had a shorter latency compared to that of normal subjects until later disease stages, whereas larger saccades showed a latency which was longer than that of normal subjects. Therefore, despite the overall prolongation of VGS latency in PD, smaller saccades of 5–10 degrees tend to be relatively facilitated. A similar trend has also been shown for hereditary progressive dystonia (HPD) in which a mild dopamine deficiency without neuronal degeneration is postulated (Terao et al., 2012). Although visually guided saccades may not be directly triggered by visual inputs, the predominance of smaller saccades may be related to the broader representation within the SC of small amplitude saccades as well as the large input it receives from cortical and subcortical areas (Sparks et al., 2000). Even if the SC were homogeneously inhibited by the excessive output from the SNr, smaller saccades would either overcome this inhibition because of their large representation, or the leaky suppression would allow small saccades to be issued, while larger saccades would be greatly suppressed. Consequently, the latency of small amplitude saccades in VGS and GS tasks would be relatively normal or even shortened compared to those of normal subjects, while large amplitude VGS or GS may be slowed in terms of latency.

As previously discussed, hypometric saccades in PD may be largely explained by the excessive SC suppression via the BG. However, considering the effect of target eccentricity referred to

above, this could be partially explained by the facilitation of small amplitude saccades, especially when their latency is short, since saccades initially programmed as large amplitude saccades may be prematurely released as small amplitude saccades.

8. Possible mechanisms for the impaired inhibition of saccades

Candidates for inhibitory pathways exerting inhibitory effects on SC include the direct inhibitory projection of the frontal eye field onto the SC, altered BG output from the SNr, actions of omnipause neurons of the midline pontine reticular formation, and the fixation cells of the SC. In the absence of pathological changes in the oculomotor structures in the brainstem and the SC at early stages of PD, the impaired inhibitory control is most likely ascribed to defective suppression of saccade-related collicular cells by the dysfunction of the fronto-nigro-collicular pathway (see Munoz et al., 2000, for review). In primates, injection of bicuculline into the SC has been shown to facilitate the initiation of saccades and an increase of irrepressible saccades made toward the center of the movement field of the SC cells at the injection site (Hikosaka and Wurtz, 1985a, 1989). In humans, patients with HPD also show an increase of saccades to cue in the MGS task (Segawa et al., 1999; Hikosaka et al., 1995; Terao et al., 2011a). Thus, a mild degree of dopamine deficiency may be associated with either an impairment of inhibitory control or “leaky” suppression from the BG (see also the previous section).

An alternative explanation for the inability to suppress unwanted saccades in a context-dependent manner would be dysfunction in the prefrontal cortex, which is presumed to project directly to the collicular saccade cells so as to exert an inhibitory control. The tonic inhibition model of Sereno (1996) suggests that, with respect to orienting, a dysfunction of prefrontal areas would release neural structures involved in reflexive saccades (e.g., the SC) from tonic inhibition, resulting in “hyper-reflexive” responses. Although the pathology of the frontal lobe is not apparent in early PD (Jellinger, 2001), functional impairment of this pathway may gradually set in as the disease progresses and then release the automatic saccade system from a top-down inhibition (Pierrot-Deseilligny et al., 2004; Crevits and de Ridder, 1997). Indeed, for the AS task, the clinical lesion study of Condy et al. (2004) showed that a direct inhibitory control of saccade triggering by the dorso-lateral prefrontal cortex (DLPFC) on the SC plays a major role in reflexive saccade suppression required for AS, rather than that by the BG or the thalamus; the number of error saccades in the AS task increased in patients in whom this pathway was impaired, which extends from the prefrontal cortex along the anterior limb, the genu, or the anterior half of the posterior limb of the internal capsule to project onto the SC. This argument is supported by studies of eye movement control in clinical populations with known prefrontal dysfunction, where deficits of response inhibition are also found (Munoz et al., 2003; Nieman et al., 2000; Reuter and Kathmann, 2004; Hodgson et al., 2007). The frequency of saccades to cue increases with the disease stage in PD (Terao et al., 2011a). This finding may be consistent with the increasing dysfunction of the prefrontal cortex in PD patients in advanced stages. It must be acknowledged, however, that uninhibited saccades to cue and short latency visually guided saccades are present in relatively early stages of the disease (Terao et al., 2011a), and the impaired inhibitory control may not be accounted for solely by the prefrontal dysfunction.

Finally, it is also possible that a compensatory increase in activity of the frontal eye field or other oculomotor cortical regions is present secondary to the increased inhibition upon the SC, and this may lead to unsuppressed saccades. It is known that movements driven by external stimuli employ different cortical routes from

those driven by an internal trigger. Behaviorally, PD patients in the advanced stage compensate for their motor deficits by using sensory guidance (Brown and Marsden, 1988). Patients are poor at suppressing prepotent behavior in response to sensory stimuli (Praagstra et al., 1998) because information from sensory stimuli relevant to the generation of a response can have rapid access to motor structures so as to facilitate prepotent movements. Structures outside the BG may compensate for the progressive loss of dopamine in PD, through, for example, overactivity of the parietal cortex. Consistent with this view, Shaikh et al. (2011) found abnormally large square wave jerks in PD patients, and ascribed them to a compensatory increase in frontal eye field activity secondary to the increased inhibition upon the SC. SC disinhibition, as indicated by the increased frequency of saccades to cue, may reflect such inputs to the SC from structures outside the BG that become active to compensate for the PD-associated changes in the BG.

In our previous study (Terao et al., 2011a), we considered the possibility that the increased level of saccades to cue in PD patients (i.e., enhancement of the reflexive system) represent balancing mechanisms recruited as a compensation for the impaired voluntary system (Sereno, 1996). If this is the case, restoration of BG function by levodopa (L-dopa) therapy should normalize the frequency of saccades to cue since recruitment of compensatory mechanisms would no longer be necessary if treatment with L-dopa restored the function of the voluntary system. According to this scheme, the frequency of saccades to cue should decrease by L-dopa therapy, but in fact this change was so small that it did not reach significance. However, L-dopa could also normalize the dopaminergic deficiency in PD and also normalize the increase in saccades to cue. We expected this since our study showed that L-dopa reversed the balance between the voluntary system (e.g., MGS) and the reflexive system (e.g., VGS), facilitating the former and suppressing the latter (Yugeta et al., 2008). In any case, L-dopa does not appear to have a significant effect on SC disinhibition as reflected in the frequency of saccades to cue.

Of course, there need not be only a single source of saccade disinhibition. van Stockum et al. (2008) suggested that there are at least two. In the AS task with a delay, timing error rates (i.e., subjects made saccades before the delay period was over), but not directional error rates, were negatively associated with neuropsychological test scores of cognitive function. On the other hand, the higher directional error rates in the AS tasks were associated with higher proportions of express saccades in the prosaccade task. Therefore, they concluded that saccadic disinhibition may not necessarily reflect a general deficit of automatic response inhibition and cognitive impairment in PD, which result in both timing and directional errors as would be caused by prefrontal dysfunction.

The notion that there need not be only a single source of saccade inhibition is supported by the treatment effects on saccade performance. STN DBS decreased the saccades to cue in MGS, but did not affect the frequency of prosaccades in AS (Yugeta et al., 2010). Occurrence of prosaccades in the AS task has been explained by the failure of the inhibitory system to effectively suppress reflexive prosaccades toward the target, especially the prefrontal cortex inhibiting the SC directly or indirectly via the descending pathway (Guitton et al., 1985; Terao et al., 1998; Condy et al., 2004; Fukushima et al., 1994; Pierrot-Deseilligny, 1991; Pierrot-Deseilligny et al., 2004; Hodgson et al., 2007), although some involvement of BG (i.e., caudate nucleus) has also been suggested for AS (Peltsch et al., 2008; Lasker and Zee, 1997; Everling and Fischer, 1998). Therefore, STN DBS may specifically affect the inhibitory mechanism of saccades mediated by the STN-SNr circuit rather than that mediated by the frontal cortex, leaving the frequency of prosaccades unaffected.

To summarize the pathophysiology of PD as discussed so far, we propose that three major drives converging on the SC determine

the saccade abnormalities in PD (Terao et al., 2011a). 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 the 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.

9. How does the treatment of PD affect saccade performance?

Since saccade parameters have a narrow normal range, saccade performance may also be used to evaluate the effect of treatment in PD (e.g., dopaminergic drugs and deep brain stimulation) on the function of the BG. The simplest prediction would be that the treatment of PD would specifically bring saccade abnormalities back toward the normal range, if not completely. Thus, the prolonged latency and decreased success rate of voluntary saccades such as MGS and AS would be normalized, while the hypometric saccades observed for all types of saccades would increase in amplitude.

Based on the scheme of Alexander and Crutcher (1990), L-dopa and dopamine agonists would be expected to improve the function of the premotor drive by altering the balance between direct and indirect pathways, while the suppression of the SC is alleviated. Similarly, although the mechanism of action of DBS is currently unknown, its effect is likened to the effect of L-dopa and would also function by altering the balance between direct and indirect pathways, leading in turn to the alleviation of the function of the motor and oculomotor loops of the BG–thalamocortical pathway. In the case of saccades, this would lead to the improved initiation of MGS via improved function of the direct pathway on the one hand (e.g., a decrease in latency and an increase in the success rate of MGS), and the increased saccade amplitudes in all oculomotor tasks through the improvement of excessive SC suppression on the other.

Previous reports on the effect of L-dopa, however, are not consistent and sometimes even conflicting. Some show no effect of dopamine treatment, whereas other studies report small effects on latency, gain or amplitude. Surprisingly, early studies showed that L-dopa, while improving motor symptoms, had little effect on saccade performance, including MGS and AS, although it improved their amplitude (Vermersch et al., 1994; Crevits et al., 2000). In contrast, Rascol et al. (1989) reported that L-dopa improves the amplitude of VGS and AS but has no effect on their latency. These inconsistencies may be due to the fact that many of these studies examined only a small number of normal subjects, who were not appropriately age-matched with the patients. This poses a great problem considering the large age-related change in saccade parameters not only during development but also for elderly subjects above 60 years of age, in whom the inter-subject variability increases greatly even in normal population (Munoz et al., 1998).

Studying a sufficient number of subjects with a reliable recording method and a more sophisticated analysis, recent studies have concurred that L-dopa and dopamine agonists shorten the latency of voluntary saccades such as MGS (Michell et al., 2006; Yugeta et al., 2008), while they prolong the latency of both externally guided saccades such as VGS (Michell et al., 2006; Yugeta et al., 2008) or of eye movements tracking the red laser dot in steps as rapidly as possible, which would also be classified as an externally triggered saccade (Hood et al., 2007), although all of these effects are relatively small. Hood et al. report decreased errors in AS, but Yugeta et al. did not observe any effect on AS.

Note that the improvement of voluntary saccades such as MGS was in the expected direction, while the delay in initiating externally triggered saccades was rather unexpected. Although it is difficult to directly explain this observation based on known physiology and anatomy, L-dopa appears to reverse the balance between the voluntary (e.g., MGS) and the reflexive systems (e.g., VGS), facilitating the former and suppressing the latter. This is consistent with the proposal of Brown et al. (1999) that visual inputs to the SC dominate “reflexive” movements by default and allow fast, visually guided saccades to take place toward a suddenly appearing target, but when a planned movement is required instead (e.g., MGS), frontal activity can suppress visually guided saccades and allow time for processing a planned response to a different target. van Stockum et al. (2012) suggested that facilitation of the reflexive saccadic system in PD is not secondary to impairment of the voluntary saccadic system; if so, facilitation of reflexive saccades should co-occur with impaired performance of voluntary saccades in patients with PD. In fact, when they measured performances of reflexive and voluntary saccades in a group of patients prescribed PD (both “on” and “off”) medication, they found strong positive correlations across reflexive and voluntary saccades in the PD group. On this basis, they concluded that the disease process of PD may affect parts of the oculomotor system which are common to reflexive and voluntary saccade generation. However, since both the latencies of reflexive and voluntary saccades may include processes which are unrelated to the BG function, the “common process” may not directly reflect the function of the BG. Although the disease process of PD may affect parts of the oculomotor system subserving both voluntary and reflexive saccade generation (e.g., SC), the effect of L-dopa may be to tip the balance in favor of the voluntary system.

The effects of L-dopa on saccade amplitude are not consistent. L-dopa improves the amplitudes of VGS and AS but it has no effect on their latencies (Rascol et al., 1989). On the other hand, Yugeta et al. (2008) demonstrated no change in the amplitude of saccades, both of VGS and MGS as well as AS, which is similar to the findings of Vermersch et al. (1994) and Crevits et al. (2000). Although there do appear to be small discrepancies among studies, the overall consensus appears to be that no great change in amplitude is induced by L-dopa. If this is true, it may indicate that L-dopa does not significantly affect the activity of the SC, which is the final common pathway for saccade generation.

Nowadays, DBS, especially of the STN, has become the mainstay of the stereotactic operation in PD. As mentioned above, the effect of DBS has been likened to the effect of dopaminergic drugs, since the benefits of DBS are usually not expected in patients who are not currently taking dopaminergic drugs. Consistently, previous studies have shown that DBS improves voluntary saccades more than it does reflexive saccades. For example, Rivaud-Péchéux et al. (2000a) showed that the gain of the first saccade and the final eye position were improved in MGS in eight bilateral STN DBS cases, while VGS was unaffected. However, Yugeta et al. (2010) studied 32 PD patients and showed changes in four different oculomotor tasks: VGS, GS (externally triggered movements), and MGS tasks, as well as AS tasks (internally triggered movements) (Fig. 5). DBS improved patients’ performance of saccade initiation in all tasks, with shorter latencies, and increased amplitudes and velocities, except for MGS latency. The improved amplitude of MGS as well as of AS was also shown by Fawcett et al. (2010). Furthermore, Kumru et al. (2004) and Sauleau et al. (2008) also showed that STN DBS enhances amplitude and shortens latency of eye (head restrained), and of eye and head (head unrestrained) in the absence of dopaminergic medication. These observations challenge the prevailing notion that DBS preferentially improves internally guided saccades but not externally guided saccades; they are both improved.

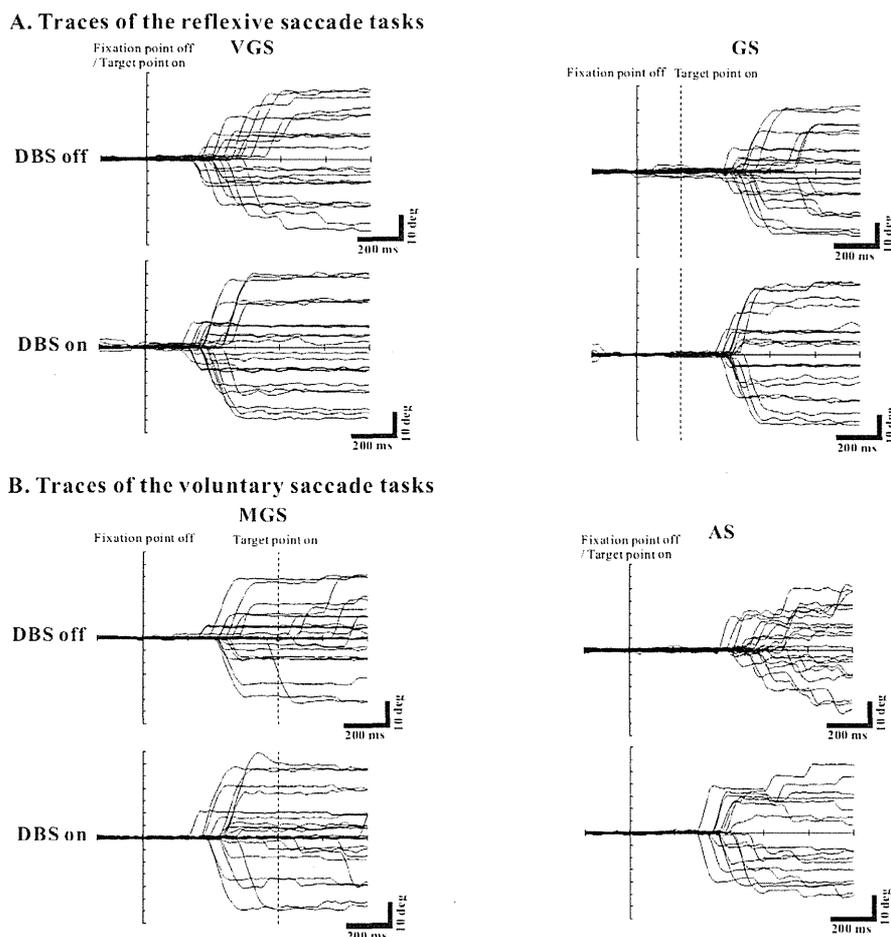


Fig. 5. The effect of STN DBS on saccades. PD patients performed four oculomotor tasks: VGS, GS (A), MGS, and AS (B). The traces show saccade recordings in a single PD patient when DBS was off (upper traces) and on (lower traces). Conventions as in Fig. 3. See the scale linked to each figure. For all tasks, the amplitude of saccades was improved when DBS was on relative to when it was off. The PD patients continued to take their regular doses of PD medication. Reproduced with permission from Yugeta et al. (2010).

The most widely-held interpretation for the effect of DBS has been that electrical stimulation of the STN, which is known to have a powerful influence on SNr, enhances both the descending facilitation passing from the cortex to the SC via the BG and also the tonic background inhibition that normally suppresses unwanted early responses (see Temel et al., 2008 for review; Antoniadis et al., 2012). To explain the observation that all types of saccades, regardless of whether they are internally or externally guided, were improved, Yugeta et al. (2010) considered these changes to be mediated by the alteration of the information processed by the SC, a pivotal visuomotor structure involved in both voluntary and reflexive saccades. Namely, STN DBS improves the amplitudes of all types of saccades by reversing the excessive inhibition of the SC toward its normal level by targeting the overactive STN-SNr circuit; STN DBS may act on the STN-SNr pathway relatively directly and normalize the function of the “bottleneck” SC, whereas it may not act primarily on the premotor drive through the direct pathway of the BG circuit. In other words, STN DBS has a more direct access to the SC than does L-dopa.

The globus pallidus (GP) is another target often selected for stereotactic surgery in PD. Until recently, few studies had been conducted that combined pallidotomy and pallidal DBS with recordings of saccade performance. Pallidotomy improves motor functions, but appears to show only limited effects on saccadic responses. Blekher et al. (2000) showed that pallidotomy decreases

the peak saccadic velocity of internally mediated saccades. Similarly, O’Sullivan et al. (2003) showed that pallidotomy disrupts ocular fixation, although there was no difference in saccadic latency or accuracy, the number of saccadic anticipations, or the ability to generate predictive saccades.

Meanwhile, pallidal DBS improved latency of reflexive saccades and delayed latency of voluntary saccades in Huntington’s disease, and also reduced patient’s ability to suppress unwanted saccades decreased with stimulation, disrupting fixation (Fawcett et al., 2005). At the moment, little is known about the role played by the GP in oculomotor control, blocked function of GPi that receive oculomotor information from the caudate nucleus was considered cause the increase in incorrect saccades, because an inability to suppress unwanted saccades is considered a failure of the volitional saccade system (Briand et al., 1999). Alternatively, because reflexive saccades are mediated by direct cortical action of the parietal and also the frontal eye field on SC (see introduction), the improved performance of VGS with DBS may be due to the restoration of visual and/or oculomotor cortical function (Fawcett et al., 2005). Because GPi sends inhibitory projections to the brainstem, it is also possible that DBS-mediated improvements are due to disinhibition of brainstem oculomotor neurons. Notably, a similar fixation instability was also demonstrated in PD patients with STN DBS (Wark et al., 2008), but Yugeta et al. (2010) showed that STN DBS decreases saccades to cue in the MGS task. Therefore, the

effect of DBS on saccade performance may vary for different targets of stereotactic surgery, but further investigation is needed in order to clarify this issue.

Although the precise mechanisms of action of various treatment modalities are unknown, saccade analysis based on the LATER model (Linear Approach to Threshold with Ergodic Rate, or saccadometry) might provide some insight into what is taking place at the neuronal level. The neuronal discharge of some saccade neurons in the frontal eye field or the SC increases gradually and triggers saccades when their activity exceeds a fixed threshold, although the threshold can vary according to the context in which saccades are made (see, for example, Hanes and Schall, 1996; Paré and Hanes, 2003; Dorris et al., 1997). Similarly in the LATER model, the latency of a single saccade in response to the target appearance can be understood as a decision process, in which saccades are triggered when the decision signal reaches a threshold. The variations in reaction time can be explained either by (i) variations in the rate of (visual) information processing or (ii) the threshold for the decision (see Carpenter, 2004; Temel et al., 2008, for review). Based on the LATER model, the effect of L-dopa on neural decision making was to increase the criterion level of evidence required before the decision to move is made (Michell et al., 2006). On the other hand, the effects of STN DBS on saccade latency can be explained by an acceleration of the processing rate of the visual information, rather than by a changing of the starting and threshold levels for decision making (Temel et al., 2008). In explaining the acceleration of the processing of the decision signal, Temel et al. suggested that electrical stimulation of the STN, which is known to have a powerful influence on SNr, enhances the descending facilitation that passes from the cortex to the SC via the BG, thus increasing the mean rate of rise of the decision signal while also decreasing the tonic background inhibition that normally suppresses unwanted early responses. Therefore, according to their theory, the effect of STN DBS is two-fold, facilitating the pre-oculomotor drive from the frontal cortex to SC and also removing the excessive inhibition of the SC. This is somewhat at variance with the findings of Yugeta et al. (2010) who suggested that the main action of STN DBS is to remove the excessive inhibition on the SC by acting on the STN-SNr pathway.

In summary, although L-dopa and other dopaminergic drugs as well as STN DBS are both effective in improving the motor symptoms of PD, their actions on the BG as well as on the relevant cortical areas differ. L-dopa changes the balance between the function of the BG in favor of the direct pathway, leading to the shortened latency and increased success rate of MGS. It does not, however, have a significant effect on saccade amplitude. In contrast, DBS, at least STN DBS, was considered to act relatively directly on the STN-SNr pathway. Thus, although the effect of DBS has generally been likened to that of L-dopa, its demonstrated effects were clearly different from those of L-dopa. These effects may be specific to STN DBS, and the effects of DBS on other targets may be different. These are certainly issues that warrants investigation in the future.

Again, these findings provide evidence against the simple dichotomy of BG function, between externally triggered and internally triggered movements, with the idea that the latter is served more by the BG, at least regarding the oculomotor pathways. Further understanding of somatomotor and oculomotor control mechanisms by the BG would be expected to enable better treatment strategies which combine electrophysiological and pharmacological approaches.

10. Behavioral correlates of the abnormal saccades in a more natural setting

Few studies to date have investigated the behavioral correlates of abnormal saccades in BG disorders in a more normal setting that

resemble daily life. In monkeys, Kato et al. (1995) and Miyashita et al. (1995) reported deficits in spontaneous saccades with local dopamine depletion in the unilateral caudate nucleus by infusion of MPTP, which could serve as a model for PD. In these monkeys, spontaneous saccades became less frequent toward the visual field contralateral to the injection, and the area scanned by the saccades became narrower and shifted to the hemifield ipsilateral to the infusion site. Although the role of the BG in spontaneous saccades, such as the ones required for visual scanning in this study, is probably nonspecific, the results were taken to suggest that local deprivation of the dopaminergic innervation in the caudate nucleus facilitates neuronal activity of the SNr leading to suppression of saccadic eye movements, which would have gated the saccades whose commands may probably originate in the cerebral cortical areas. In an accompanying paper, Kori et al. (1995) showed in the same monkeys that the latency was consistently prolonged for the contralateral MGS. The amplitude and velocity of saccades also decreased in a contralateral direction, both for MGS and VGS.

In humans, Matsumoto et al. (2011) reported the visual scanning pattern of the gaze when subjects inspected pictures of varying complexity for later recall (Fig. 6). The heads of the subjects were fixed, and saccades were needed to explore the picture. Regardless of the complexity of the picture, patients scanned the picture with smaller amplitude saccades compared to normal subjects, and they subsequently ended up exploring a smaller area of the picture. Interestingly, the smaller area scanned was most prominent with simpler pictures and the patients approached normal behavior as the pictures viewed became more complex (see also Terao et al., 2002). Nevertheless, the area covered by PD patients' gaze was still smaller than that for normal subjects. Patients also made fewer saccades and had longer fixation times, just as in the MPTP-injected monkeys of the Kato et al. (1995) and Miyashita et al. (1995) study, but the smaller area scanned was mainly ascribed to the small amplitude of saccades during the visual exploration. Therefore, similarly to the monkeys above, the potential saccadic signals impinging on the SC would be gated in PD patients in whom the SC is excessively inhibited by the increased BG output, thus leading to the hypometria of saccades and narrower areas scanned.

Importantly, the scanned area significantly correlated with the saccade amplitude in most images. Matsumoto et al. (2012) went on to correlate the parameters of saccade visual scanning in this task with those obtained in more conventional oculomotor tasks (VGS and MGS), which were reduced in both cases. Only the amplitude of MGS, but not that of VGS, correlated significantly with the saccade amplitude during the visual exploration of pictures in the same subjects. These results may indicate that BG dysfunction could reduce the amplitude of saccades made during visual scanning, which are generated with a mechanism similar to that of voluntary saccades. Although the exact neural mechanism for generating scanning saccades is unknown, primate studies demonstrated that some cells related to MGS in the caudate nucleus, located in the input portion of the BG that is related to eye movement, were also found to discharge while the monkey was searching for a visual target (Hikosaka et al., 1989). Hallett (2011) argued that what Matsumoto observed in PD patients may represent a counterpart of bradykinesia and/or akinesia for gaze movements.

Of course, the above is but one example of behavioral correlates of the abnormal saccades in PD. Since the experiments of Matsumoto et al. (2011) were all conducted in the "on" state, more studies are warranted to determine what would happen under treatment, such as L-dopa therapy or DBS. Saccade measurements in PD would serve to clarify the treatment effects very clearly under similar ecological settings.

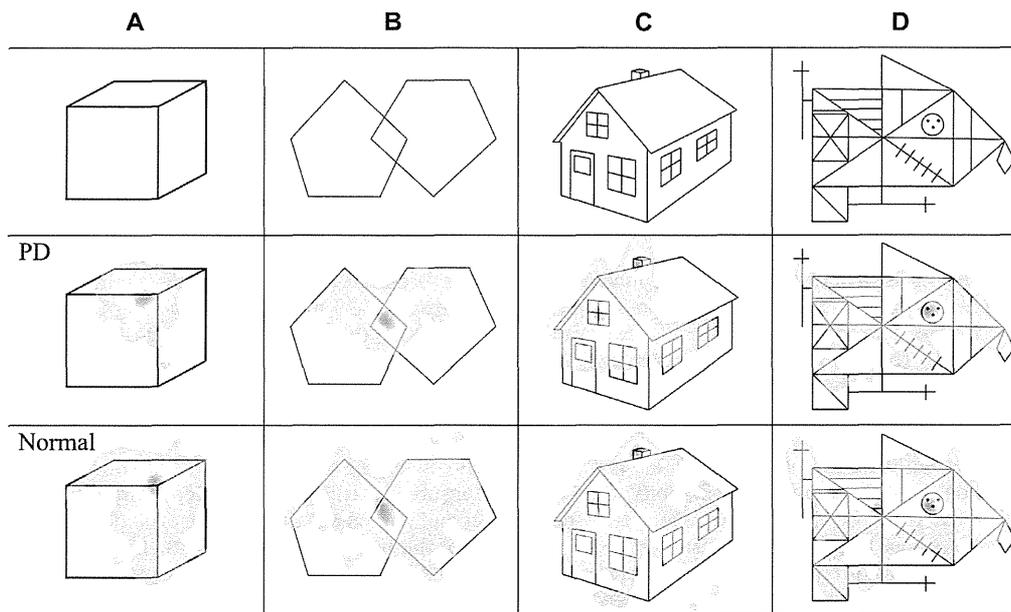


Fig. 6. Ocular bradykinesia impairs visual exploration in Parkinson's disease. The figures show color-coded maps (heat maps) of the distribution of fixation when normal subjects and PD patients view pictures of increasing complexity (from left to right). A: image 1 (a cube), B: image 2 (two pentagons combined in different orientations), C: image 3 (a house), D: image 4 (the Rey–Osterrieth complex figure). Heat maps, or graphical color-coded maps showing the distribution of eye-fixation positions, were created for each image. Heat maps color-coded in red, yellow, and green according to the duration of fixation were overlaid onto each of the images. The upper panels show the images presented to the subjects. The middle panels show the heat maps in PD patients and the lower panels those in normal subjects. In all images, the distribution of eye-fixation position (green-colored area) in PD patients was narrower than that in normal subjects. Reproduced with permission from Matsumoto et al. (2011).

Another behavioral correlate of interest would be whether the saccade abnormality could affect patient's stance or postural instability. The inability to generate saccades can compromise safe ambulation, since anticipatory saccades should occur normally in situations that involve changing the direction of walking (Hollands et al., 2002) or prior to obstacle avoidance (Di Fabio et al., 2003). When saccades are not generated infrequently, there is an increase in risk for falling (Di Fabio et al., 2005). There are also reports on the improvement of gaze control after balance and eye movement training in patients with progressive supranuclear palsy (Zampieri and Di Fabio, 2009). Although these findings may hold to some extent to PD, as yet there are only a limited number of studies presumably because ocular motility is relatively mild in the early stages of this disorder. Anastasopoulos et al. (2011) found an altered eye-to-foot coordination in standing parkinsonian patients during large gaze and whole-body reorientations. When standing early PD patients could reorient eyes and body to illuminated targets of eccentricities up to ± 180 degrees, they were able to assemble multisegmental movements of the eyes, head, trunk, although trunk dyskinesia prolonged the target acquisition time. Preserved eye motion was used to compensate for the trunk slowness. However, since the deficit in ocular motility becomes a problem at relatively advanced stages of PD, postural instability and falls may aggravate when this compensation breaks down as the disease progresses.

11. Basal ganglia dysfunction in Parkinson's disease as viewed from saccade performance

We have discussed above how the SC serves as a "bottleneck" for all kinds of volitional saccades. The excessive inhibition of the SC would also affect the performance of not only voluntary but also of reflexive saccades, and prolong the latency of all types of saccades mediated by SC. Some researchers point out that this

classical model is too limited to account for recent evidence emerging from primate studies (Watanabe and Munoz, 2011), although as we have seen, at least in the clinical setting, the classical model of the BG circuit is quite good at explaining most of the saccade abnormalities in PD. Still, we need to revise this classical model to account for some aspects of recent findings, especially the impairment of inhibitory control of saccades in PD.

We would like to point out that there are at least two major limitations to the classical model that need to be overcome in order to accommodate all the findings of saccade abnormalities. The first is the limitation of the rate or the tonic inhibition model of the BG. The model posits that in PD, the high frequency activity of the SNr excessively suppresses the SC. This leads to the prediction that the saccades to cue would decrease. Indeed, what we observe in PD is quite the opposite of this (see above). Furthermore, our previous study showed that STN DBS decreases the frequency of saccades to cue (Yugeta et al., 2010), meaning that it restores the function of the BG in inhibitory saccade control. Again, if, as discussed above, STN DBS acts directly on the STN-SNr pathway and restores the excitability of the SC from excessive inhibition, we would rather expect that STN DBS should increase the frequency of saccades. To overcome this apparent contradiction, we have interpreted this finding as consistent with a view that STN DBS may set the functional level of the SC appropriate both for saccade initiation and inhibition through this pathway by normalizing the excitability of the SC (Yugeta et al., 2010), thereby decreasing the occurrence of saccades to cue. However, the exact mechanism by which inhibitory control of movement is implemented in the normal brain and what makes it abnormal under dopamine deficient states cannot be explained clearly under the rate model.

Departing from the classical rate model, we should take into consideration not only the "rate" of BG activity but also its pattern (Brown, 2003). A pathological task-related modulation of oscillation within the BG is one possible explanation for the impairment of the inhibitory control of saccades. In normal

monkeys performing a saccade task toward a visual target, local field potential synchronization in the β range also showed a task-related decrease, but only for recording sites that were directly engaged in the task (Courtemanche et al., 2003). This suggested that local field oscillations serve the function of filtering striatal input–output transmission (Hutchison et al., 2004). This is also the case with voluntary movements of the hand; β band oscillations are reduced prior to and during self- and externally paced voluntary movements (Cassidy et al., 2002; Williams et al., 2003; Kühn et al., 2004; Doyle et al., 2005; Kempf et al., 2007). Conversely, increased β activity is involved in movement inhibition; in a go/no-go task, the β suppression following the go/no-go signal was prematurely terminated and reverted to an early β power increase (Kühn et al., 2004). There is growing evidence that PD is associated with pathological synchronous oscillatory activity in the BG, primarily in the β range (11–30 Hz) (Bergman et al., 1998; Wichmann et al., 1999a,b; Nini et al., 1995; Raz et al., 1996; Brown, 2003). Recently, Sarma et al. (2012) showed that cues suppress pathological BG activity (β -oscillations) in STN through activation of the corticostriatal pathway. In a two-step motor task, subjects were told to perform a joy-stick movement either in response to a cue presented at a predicted and unpredicted time, or when no cue was presented at a predicted time and subjects had to make a self-initiated movement instead. The decrease in β -oscillations and increase in directional tuning (i.e., the neurons are more likely to fire in one direction more than at least one other direction) was observed only when a cue was presented at a predicted time and when subjects had to initiate a self-triggered movement when no cue was presented at the predicted time. In contrast, no modulation of oscillation and directional tuning was found during trials in which cues were presented at an unpredicted time. This pattern of results suggests that during motor planning either a predictably timed external cue or an internally generated cue (i.e., generated by the absence of a cue) trigger the execution of a motor planning in the premotor cortex, whose increased activation then suppresses pathological activity in STN through direct pathways, leading to motor facilitation in PD. If the modulation of activity is compromised, this would result in an inability to suppress unwanted saccades to the visual signal.

It should be noted, however, that neither tonic nor phasic disinhibition related to oscillatory activity in the BG can explain why the timing of periods of low inhibition just happen to coincide with the time when saccades to cue might take place involuntarily in the MGS task; a phasic disinhibition can occur any time after the presentation of the cue if this is caused by the ongoing oscillation. Therefore, introducing the abnormal discharge pattern in the BG and other neural structures still does not totally explain the defects in saccade inhibition. The precise mechanism warrants future investigation.

Another important limitation of the model is the role of BG in modulating saccades in a context dependent manner (Vokoun et al., 2011). Basso and Liu (2007) demonstrated that SNr stimulation results in only subtle effects on visually guided saccades, whereas it has more profound effects on MGS (i.e., saccades made in the absence of visual cue), also reducing the likelihood of its successful performance by around 10%. Furthermore, electrical stimulation of the SNr causes reliable reduction of the activity of SC build-up neurons, although it also leads to a decrease in saccade latency with reduced variability (Liu and Basso, 2008). During some tasks, SNr and SC neuronal activity are not mirror images of each other (Basso and Wurtz, 2002). To explain the apparent discrepancy in effects, Basso et al. suggested that the SNr initially inhibits saccade-related activity in build-up and burst neurons of the SC through its direct inputs and then disinhibits the SC via inhibitory interneurons.

Accumulating evidence suggests that, rather than simply serving to generate a saccade, both the SNr and the SC may play a role closer to saccade target selection. For example, Basso and Wurtz (1997, 1998, 2002) found that some neurons in the SC reflect changes in the probability that a particular target will be identified for saccade generation; the higher the probability that a particular location will be selected as a saccade target, the larger and longer will be the pause in SNr neuronal activity preceding saccade generation. Thus, the SNr may play a role in target selection because the pause predicted saccade choices independent of the cue and sometimes occurred well before saccade initiation (see Schall and Thompson, 1999 for review). Invoking the formulation of Jeannerod (2006), this implies that the goal of the saccades which are represented in the SC may not correspond to the actual state of the world, but rather corresponds to a possible state of saccade generation which will arise if the saccade were effective. Rather than directly issuing motor output for saccades, the multiple inputs converging onto the SC could be conceived of as an “interface” to ensure versatility of action depending on the context (i.e., to select and implement the possible candidate of motor outputs in favor of the most appropriate for the situation in which the motor action is to be executed, and then switching off the other alternatives). In the case of saccades, this allows one to turn their gaze immediately in the direction of the visual signal, delay the execution of the saccade instead of responding to it immediately, look in the direction where there is no visual input, or even select from among more than one potential target. While some types of saccades, such as MGS, are directly driven by the “double inhibition” pathway through the frontal cortex-caudate-SNr-SC, it is important to remember that the main function of the BG is not to directly implement concrete motor outputs but to modulate functional processes occurring outside the BG. In order to see how these new findings in basic neuroscience can be reconciled with the clinical findings, the role of the STN-SNr pathway in generating volitional saccades may need to be reconsidered in light of the new perspectives as discussed in the present review.

In summary, we have shown that saccade performance could be used to probe the dysfunction of BG in PD. Instead of the widely-held dichotomy of impaired voluntary versus relatively spared reflexive saccades in PD, most of the saccade abnormalities in PD could be explained by postulating various drives converging on the SC, including those from the BG. The differential treatment effects of L-dopa and DBS suggested that the various treatment modalities target different parts of the BG circuit the oculomotor system. On the other hand, some saccade abnormalities such as the impairment in inhibitory control of saccades still remain to be explained. Further elucidation the pathophysiological basis of PD and the mechanism of action of various therapies will be useful in establishing more effective treatment strategies in this disorder, and enable us to use eye movement recording as an indicator of treatment effects.

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Relationship between cognitive impairment and white-matter alteration in Parkinson's disease with dementia: tract-based spatial statistics and tract-specific analysis

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Abstract

Objectives We investigated the relationship between white-matter alteration and cognitive status in Parkinson's disease (PD) with and without dementia by using diffusion tensor imaging.

Methods Twenty PD patients, 20 PDD (Parkinson's disease with dementia) patients and 20 age-matched healthy controls underwent diffusion tensor imaging. The mean diffusivity and fractional anisotropy (FA) map of each patient group were compared with those of the control group by using tract-based spatial statistics. Tractography images of the genu of the corpus callosum fibre tracts were generated, and mean diffusivity and FA were measured.

Results FA values in many major tracts were significantly lower in PDD patients than in control subjects; in the prefrontal white matter and the genu of the corpus callosum they were significantly lower in PDD patients than in PD

patients. There was a significant correlation between the Mini-Mental State Examination (MMSE) scores and the FA values of the prefrontal white matter and the genu of the corpus callosum in patients with PD.

Conclusions Our study shows a relationship between cognitive impairment and alteration of the prefrontal white matter and genu of the corpus callosum. These changes may be useful in assessing the onset of dementia in PD patients.

Key Points

- Dementia is a common and important non-motor sign of Parkinson's disease (PD).
- The neuropathological basis of dementia in PD is not clear.
- DTI shows abnormalities in the prefrontal white matter in PD with dementia.
- Prefrontal white matter alteration may be useful biomarker of dementia in PD.

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Keywords Dementia · Diffusion tensor imaging · Parkinson's disease · Tract-based spatial statistics · Tract-specific analysis

Abbreviations

DTI	Diffusion tensor imaging
FA	Fractional anisotropy
HSD	Honestly significant difference
MD	Mean diffusivity
MMSE	Mini-Mental State Examination
PD	Parkinson's disease
PDD	Parkinson's disease with dementia
TBSS	Tract-based spatial statistics

Introduction

Dementia, one of the most common and important non-motor signs of Parkinson's disease (PD), greatly affects functioning and quality of life [1]. Cognitive impairment in PD occurs even at the early stage [2], and a recent longitudinal study that followed newly diagnosed PD patients for 20 years suggests that up to 80 % will develop dementia [3]. However, despite the clinical importance of dementia, its neuropathological basis in PD remains controversial [4].

According to the hypothesis proposed by Braak et al. [5], deposition of Lewy bodies and Lewy neurites, which pathologically characterises PD, begins in the brain stem, spreads to the forebrain and limbic system, and finally reaches the neocortex. The pathological characteristics are divided into six subgroups according to the deposition of the Lewy bodies. These stages and the progression of cognitive impairment occur in parallel [6].

Many demographic and clinical characteristics have been evaluated as potential risk factors for the development of dementia in PD. Advanced age, relatively severe parkinsonism and mild cognitive impairment [7] have been identified as risk factors in several longitudinal studies [8]. Although demographic and clinical characteristics can be used to help estimate variations in the rate of cognitive decline and time to dementia in PD, objective biomarkers (such as magnetic resonance imaging [MRI] findings) are also needed.

In structural MRI studies, patients who have Parkinson's disease with dementia (PDD) have atrophy of the parieto-temporal lobe, entorhinal cortex, hippocampus, prefrontal cortex and posterior cingulate, unlike PD patients without dementia or healthy controls [9–11].

There have also been reports of a relationship between cognitive status and white-matter alteration as determined by using diffusion tensor imaging (DTI). DTI can be used to measure the characteristics of local microstructural water diffusion in brain tissue. One representative diffusion tensor parameter is FA, which describes the degree of water molecule anisotropy or the directional preference of the water diffusion process. FA values in white matter are determined mainly by the cytoskeleton of the neurofilaments and microtubules and by the axonal membrane [12]. FA abnormalities in the brain are interpreted pathologically as being caused by loss of neurons or glia, by gliosis or demyelination [13], or by loss of the structural integrity of the white matter (i.e. white-matter damage) [14]. Wiltshire et al. [15] reported a significant correlation between Mini-Mental State Examination (MMSE) score and mean diffusivity (MD) within the corpus callosum, Matsui et al. [16] reported that decreased fractional anisotropy (FA) values in the parietal white matter are associated with executive dysfunction, and Hattori et al. [14] reported that FA values in the parietal white matter

significantly correlated with MMSE scores in patients with PD.

Wiltshire et al. [15] used tractography in their analysis, whereas Matsui et al. [16] used the region of interest (ROI) method. Both tractography and the ROI method have limitations in that their analytical domains are confined to fixed areas and it is difficult to prevent analyst bias. Hattori et al. used tract-based spatial statistics (TBSS) to perform a whole-brain analysis; for DTI they used 1.5-T MRI with a relatively small number of motion probing gradient (MPG) axes [12].

From these previous studies, we hypothesised that the changes in white matter in PDD patients are linked to cognitive impairment. We therefore performed a whole-brain analysis by using TBSS; for the DTI we used 3-T MRI, and we increased the number of MPG axes to 32 in an effort to overcome the limitations of previous studies.

After detecting specific white-matter alterations by using the TBSS method, we performed a more detailed investigation of the alteration by using tractography.

Materials and methods

Subjects

This study was approved by an institutional review board; informed consent was obtained from all participants before evaluation. For subjects who were deemed by the clinician not to have the capacity to give consent, a legally authorised surrogate provided consent.

There were 60 subjects: 20 PD patients, 20 PDD patients and 20 healthy controls. Note that some of these patients had also participated in our previous study [17]. All PD patients had been diagnosed by neurologists and met the United Kingdom Parkinson's Disease Society Brain Bank criteria [18]. PD was staged according to the Hoehn and Yahr scale, and the subjects underwent the Japanese version of the MMSE to assess cognitive dysfunction [19]. PDD was diagnosed in accordance with recently published guidelines [20], and patients with probable PDD were selected. All PD and PDD patients were taking levodopa (Table 1) at the time of the MRI and clinical examination.

Twenty-four months or more after MRI, all of the patients remained free of atypical parkinsonism and continued responding satisfactorily to anti-parkinsonian therapy. The 20 normal control subjects were recruited from the general population and were carefully matched by age with the patients. Individuals with any history of hypertension, diabetes mellitus, cardiovascular disease, stroke, brain tumour, epilepsy, Parkinson's disease, dementia, depression, drug abuse or head trauma were excluded as controls.

The demographic characteristics of the subjects are shown in Table 1.

Table 1 Demographic characteristics of the subjects

	Control (<i>n</i> =20)	PD (<i>n</i> =20)	PDD (<i>n</i> =20)	<i>P</i> value
Sex, male : female	10 : 10	8 : 12	10 : 10	NS
Age in years, mean (SD)	72.7 (3.3)	71.6 (4.3)	71.7 (5.3)	NS
Disease duration in months, mean (SD)	NA	94.0 (53.4)	146.6 (91.0)	<0.05 (PD vs PDD)
Hoehn–Yahr stage (SD)	0	2.4 (1.0)	2.9 (0.7)	<0.05 (PD vs PDD)
MMSE (SD) ^a	28.8	25.7 (3.2)	18.7 (5.8)	<0.01 (PD vs PDD)
Levodopa dosage mg/day, median (SD)	0	464.2 (175.0)	673.3 (120.0)	<0.05 (PD vs PDD)

PD Parkinson's disease, PDD Parkinson's disease with dementia, MMSE Mini-Mental State Examination, NA not applicable, NS not significant ($P>0.05$)

^aMMSE scores were significantly lower in PDD patients than in controls ($P<0.01$) or PD patients ($P<0.01$), but the scores did not differ significantly between controls and PD patients

MRI

MRI was performed at 3-T (Achieva; Philips Medical Systems, Best, The Netherlands) using an eight-channel phased-array head coil for sensitivity encoding parallel imaging. Conventional MR images, such as T1-weighted spin echo images, T2-weighted turbo-spin echo images and fluid-attenuated inversion recovery images, were obtained before acquisition of the diffusion tensor images. DTI was performed by using the spin-echo echo-planar technique (TR/TE 5,443/70 ms, matrix size 128×128, field of view 224×224 mm², slice thickness 3 mm with no gap). Images were obtained with both 32-direction diffusion-encoding ($b=1,000$ s/mm² for each direction) and no diffusion encoding ($b=0$ s/mm²). A total of 50 axial section images were obtained, covering the whole cerebrum. MR data acquisition time was 7 min 17 s.

DTI image processing using TBSS

Voxel-based analysis of the DTI data was performed using TBSS (tract-based spatial statistics) [21] implemented with the FMRIB Software Library 4.1.5 (FSL, Oxford Centre for Functional MRI of the Brain, UK; www.fmrib.ox.ac.uk/fsl). After eddy current correction and brain extraction had been performed, FA and MD images for all subjects were created by fitting a tensor model to the raw diffusion data. FA images of all subjects were aligned in standard Montreal Neurological Institute (MNI152) space by using FNIRT, a non-linear registration tool that uses a B-spline representation of the registration warp field.

Next, the mean FA image was created and thinned to create the mean FA skeleton, which represented the centres of all tracts common to the groups. The mean FA skeleton was thresholded to FA>0.20 to include the major white-matter pathways but exclude peripheral tracts and grey matter. Each subject's aligned FA map was then projected onto this skeleton by assigning to each point on the skeleton

the maximum FA in a plane perpendicular to the local skeleton structure. The resulting skeletons were fed into voxel-wise statistics.

By applying the original non-linear registration of each subject's FA to the standard space, the MD was also projected onto the mean FA skeleton. The MD data were also used to calculate voxel-wise statistics.

Voxel-wise statistics of the skeletonised FA data were applied by using Randomise (part of FSL) to test for group differences between the patient and control groups. Randomise performed permutation-based testing with 5,000 permutations and inference by using TFCE (threshold-free cluster enhancement) [22] with a threshold of $P<0.05$, corrected for multiple comparisons by using the family-wise error correction.

Randomise was also used to examine the relationship between FA/MD and MMSE score, disease duration, Hoehn–Yahr stage, levodopa dosage in the PD and PDD patients group separately and combined, by using multiple linear regression analysis ($P<0.05$, corrected for gender and age at the time of MRI).

The anatomical locations of regions with significant group differences in FA and MD on the white-matter skeleton were identified by using a white-matter atlas [23].

DTI image processing using tract-specific analysis

DTI data were transferred to an offline workstation. Maps of FA and MD were computed by using dTV II and VOLUME-ONE 1.72, developed by Masutani et al. [24] (University of Tokyo; diffusion tensor visualiser available at <http://www.volume-one.org/>), Diffusion tensors were computed, and fibre tracts were created by using interpolation along the z-axis to obtain data (voxel size 2.0×2.0×3.0 mm³). Colour-coded maps were created by using 33 sets of images (32 sets with $b=1,000$ s/mm², 1 set with $b=0$ s/mm²). On the colour maps, red was assigned to left–right, green to anteroposterior and blue to the craniocaudal direction. Fibre tracts were based on the fibre assignment made by using the continuous tracking