Probing basal ganglia functions by saccade eye movements

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Abstract
The basal ganglia (BG) are a group of subcortical structures involved in diverse functions, such as motor, cognition and emotion. However, the BG do not control these functions directly, but rather modulate functional processes occurring in structures outside the BG. The BG form multiple functional loops, each of which controls different functions with similar architectures. Accordingly, to understand the modulatory role of the BG, it is strategic to uncover the mechanisms of signal processing within specific functional loops that control simple neural circuits outside the BG, and then extend the knowledge to other BG loops. The saccade control system is one of the best-understood neural circuits in the brain. Furthermore, sophisticated saccade paradigms have been used extensively in clinical research in patients with BG disorders as well as in basic research in behaving monkeys. In this review, we describe recent advances of BG research from the viewpoint of saccade control. Specifically, we account for experimental results from neuroimaging and clinical studies in humans based on the updated knowledge of BG functions derived from neurophysiological experiments in behaving monkeys by taking advantage of homologies in saccade behavior. It has become clear that the traditional BG network model for saccade control is too limited to account for recent evidence emerging from the roles of subcortical nuclei not incorporated in the model. Here, we extend the traditional model and propose a new hypothetical framework to facilitate clinical and basic BG research and dialogue in the future.

Introduction
The basal ganglia (BG) are a group of subcortical structures involved in diverse functions, such as motor, cognition and emotion (Alexander & Crutcher, 1990; Mink, 1996; Hikosaka et al., 2000, 2006; Nicola, 2007; Humphries & Prescott, 2010). These functions are achieved by tight interconnections with virtually all cortical areas as well as important subcortical structures. Because the BG are important for many aspects of everyday behavior, BG dysfunctions cause a wide variety of behavioral deficits observed in neurological and psychiatric disorders, such as Parkinson’s disease (Bergman et al., 1998; Obeso et al., 2000) and schizophrenia (Carlsson & Carlsson, 1990; Menon et al., 2001; Howes & Kapur, 2009).

Because of the importance of the BG for normal and abnormal behavior, extensive studies have been carried out to understand BG functions in system neuroscience. Although significant advances have been made since the proposal of the seminal conceptual model of the BG two decades ago (Albin et al., 1989; DeLong, 1990), we are still struggling to understand how BG neural circuits control behavior. One of the difficulties in addressing this issue is that the BG do not control concrete functions directly, such as perception or action, but rather modulate functional processes occurring in structures outside the BG (e.g. Frank, 2005). Accordingly, to understand this unintuitive modulatory role of the BG, we should take advantage of one system that is well understood.

Here, we propose that the saccade control system is advantageous for exploring the role of the BG in behavioral control because of the following three reasons. First, the saccade control system is one of the best-understood neural circuits in the brain (Scudder et al., 2002; Sparks, 2002; Munoz & Everling, 2004; Schall, 2004). Second, saccades have been used extensively in clinical studies in patients with BG disorders (Everling & Fischer, 1998; Leigh & Kennard, 2004; Munoz et al., 2007; Gooding & Basso, 2008) as well as in basic studies in behaving monkeys (Hikosaka et al., 2000; Shires et al., 2010), which provides an interesting opportunity to link between clinical and basic studies using the same behavioral control system. Third, the diverse functions of the BG are presumably mediated by...
their parallel functional cortex–BG loops with similar anatomical architectures (Alexander & Crutcher, 1990; Mink, 1996; Hikosaka et al., 2000; Nicola, 2007; Humphries & Prescott, 2010). Therefore, by understanding how the functional loops for saccade control work, we can extend the knowledge to other functions mediated by different cortex–BG loops.

In this review, we describe recent advances in BG research from the viewpoint of saccade control. Specifically, we try to account for experimental results from neuroimaging (functional magnetic resonance imaging and positron emission tomography) and clinical [lesions and deep brain stimulation (DBS)] studies in humans based on the updated knowledge of BG functions derived from neurophysiological experiments in behaving monkeys. By summarizing the potential role of each BG nucleus in saccade control, we raise issues regarding BG research that need to be addressed in future. We first describe saccade paradigms used extensively to evaluate saccade behavior and neural circuits controlling saccades. We then discuss the potential role of each BG nucleus in saccade control.

**Saccade paradigms**

Saccade paradigms that have been used extensively in clinical studies in patients with BG disorders and basic studies in behaving monkeys are summarized in Fig. 1. In a prosaccade paradigm (Fig. 1A), subjects maintain their eyes on a central fixation point. After a peripheral visual stimulus appears, they initiate a saccade toward the stimulus. In an antisaccade paradigm (Fig. 1B) (Hallett, 1978; Munoz & Everling, 2004), everything is the same as in the prosaccade paradigm, except that subjects are required to generate a goal-directed saccade to the opposite location of the peripheral visual stimulus. Subjects sometimes generate an automatically triggered saccade toward the stimulus (blue arrow in Fig. 1B) instead of making a volitional antisaccade toward the opposite location (red arrow in Fig. 1B) (Fischer & Weber, 1992; Bell et al., 2000; Dafoe et al., 2007). These inappropriate saccades are called direction errors. In a visual delay saccade paradigm (Fig. 1C), subjects are not allowed to generate a saccade toward the peripheral visual stimulus until the fixation point disappears. In a memory delay saccade paradigm (Fig. 1D) (Hikosaka & Wurtz, 1983a), the peripheral visual stimulus appears only briefly. Therefore, subjects must memorize the stimulus location and generate a saccade toward it only after the fixation point disappears. During the visual and memory delay saccade paradigms, subjects sometimes initiate a saccade immediately after the appearance of the peripheral visual stimulus (blue arrows in Fig. 1C and D) (Crevits & De Ridder, 1997; LeVasseur et al., 2001; Chan et al., 2005; Gurvich et al., 2007; Yugeta et al., 2010). These inappropriate saccades are called timing errors. In patients with BG disorders, abnormal saccade behavior can be seen in the frequency of direction and timing errors as well as in the latencies of saccades (reaction times) from task events instructing subjects to initiate saccades (stimulus appearance in pro- and antisaccades and fixation point disappearance in visual and memory delay saccades) (Everling & Fischer, 1998; Leigh & Kennard, 2004; Munoz & Everling, 2004; Gooding & Basso, 2008).

**Saccade control system**

We describe briefly the neural circuits in the saccade control system that are modulated by the BG. Saccades are controlled directly by the brainstem saccade burst generator circuits (Scudder et al., 2002; Sparks, 2002). These circuits are driven mainly by saccade commands issued by the superior colliculus (SC) in the midbrain. The frontal eye field (FEF) in the cerebral cortex also sends projections to the brainstem in addition to the SC, although the functional significance of the former connections is unclear (Hanes & Wurtz, 2001). The SC and FEF are necessary for saccade initiation because lesions in both structures abolish saccade generation (Schiller et al., 1980). Some neurons in the SC and FEF increase activity gradually and trigger saccades when their activity reaches a fixed threshold for saccade initiation (Hanes & Schall, 1996; Munoz & Schall, 2003; Pare & Hanes, 2003), although the exact threshold might depend on task demands (Everling et al., 1999; Everling & Munoz, 2000). The firing characteristics of SC and FEF neurons before saccade initiation correspond well to several cognitive models designed to explain the distribution of reaction times (Trappenberg et al., 2001; Usher & McClelland, 2001; Reddi et al., 2003; Ratcliff & McKoon, 2008). Such correspondence is not seen in neural circuits controlling limb movements (Churchland et al., 2006).

Figure 2 shows an example of the simple cognitive models that can account for the distribution of reaction times [linear approach to threshold with ergodic rate (LATER) model] (Carpenter & Williams,

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**Fig. 1. Saccade paradigms.** Prosaccade (A) and antisaccade (B) paradigms. After subjects fixate on the central fixation point, a stimulus appears. Subjects generate a saccade toward the stimulus (prosaccade) or toward the opposite of the stimulus (antisaccade). During the antisaccade paradigm, subjects sometimes generate an inappropriate saccade toward the stimulus (red arrow – direction error). Visual (C) and memory (D) delay saccade paradigms. In these paradigms, subjects need to maintain fixation on the central fixation point after stimulus appearance. They are allowed to generate a saccade after the central fixation point disappears. During the memory delay saccade paradigm (D), the stimulus appears only briefly. Therefore, subjects need to memorize the location of the stimulus. During the visual and memory delay saccade paradigms, subjects sometimes generate an inappropriate saccade in response to stimulus appearance (red arrows – timing errors).
The model assumes a constant baseline activity and linear rise of a decision signal. Saccades are triggered when the decision signal reaches a threshold. According to this model, reaction times can be prolonged or shortened by changing one of the following parameters: the average ‘rate of rise’ and ‘distance’ between the baseline and threshold. An example of LATER model fittings to reaction time distributions during the prosaccade paradigm without (B) and with (C) electrical microstimulation delivered to the CN. The model fitted to the data assumes that microstimulation changed the rate of rise. This fitting result is better than another model assuming that microstimulation changed the distance between the baseline and threshold (not shown) (for details, see Watanabe & Munoz, 2010a).

In the following sections, we describe how each BG nucleus contributes to saccade control. We divide the sections into two parts. First, we summarize the functional organization of BG nuclei traditionally assigned for saccade control (Traditional saccade control circuit in the basal ganglia) (Fig. 3). Second, we show accumulating evidence suggesting that other BG nuclei not incorporated in the traditional BG model are potentially involved in saccade control (Extended saccade control circuit in the basal ganglia) (Fig. 6). Note that several important anatomical connections are omitted in Figs 3 and 6 to retain simplicity. We describe these additional anatomical connections in the text when necessary.

### Traditional saccade control circuit in the basal ganglia

Figure 3 shows how the traditional BG model controls the SC and FEF to influence saccade initiation (Hikosaka et al., 2000). The major components of this traditional BG model are the substantia nigra pars reticulata (SNr), CN, subthalamic nucleus (STN) and external segment of the globus pallidus (GPe). We update the potential role of these BG nuclei in saccade control inferred from neuroimaging and clinical studies in humans and neurophysiological studies in behaving monkeys by taking advantage of homologies in saccade behavior.

#### Substantia nigra pars reticulata

**Basic characteristics**

The SNr is the main output structure of the BG for saccade control (Fig. 3) (Hikosaka et al., 2000). The signals in the SNr influence saccades by controlling the SC directly and the FEF and other cortical saccade areas, such as the supplementary eye field and lateral intraparietal area, indirectly via the thalamus (Hikosaka et al., 2000). Because SNr neurons are GABAergic, their tonic activity imposes continuous inhibition on the SC and thalamus and suppresses saccade

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Fig. 2. An example of saccade models. (A) LATER model. The saccade decision signal builds up linearly from the baseline until it reaches the threshold for saccade initiation. The distribution of saccade reaction times is generated because the rate of rise for saccade decision signals is chosen randomly from the normal distribution on each trial. Reaction times can be shortened or prolonged by changing one of the following parameters: the average ‘rate of rise’ and ‘distance’ between the baseline and threshold. An example of LATER model fittings to reaction time distributions during the prosaccade paradigm without (B) and with (C) electrical microstimulation delivered to the CN. The model fitted to the data assumes that microstimulation changed the rate of rise. This fitting result is better than another model assuming that microstimulation changed the distance between the baseline and threshold (not shown) (for details, see Watanabe & Munoz, 2010a).
initiation (Hikosaka & Wurtz, 1983a,b,c,d, 1985a,b). It has been suggested that SNr neurons facilitate and suppress saccade initiation by either decreasing or increasing activity from their tonic firing rates, respectively (Handel & Glimcher, 1999; Basso & Wurtz, 2002; Sato & Hikosaka, 2002). Although the SNr projects mainly to the SC and thalamus in the same hemisphere and controls the initiation of contralateral saccades, it also projects to the SC and thalamus in the opposite hemisphere (Jiang et al., 2003; Cebrian et al., 2005) and presumably also suppresses the initiation of ipsilateral saccades (Jiang et al., 2003).

**Hyperkinesia**

In neurophysiological studies with clinical patients, the output signals of the BG have been analyzed extensively in the skeleton motor BG by recording neural activity from the internal segment of the globus pallidus (GPi), corresponding to the SNr in the oculomotor BG (Alexander & Crutcher, 1990; Mink, 1996). We therefore describe the firing characteristics of GPi neurons briefly, and then discuss abnormal saccade behavior in patients with hyperkinetic disorders and the potential role of the SNr in saccade control.

Neurons in the GPi have abnormally low frequency activity in patients with involuntary movements due to hyperkinetic disorders, such as Huntington’s disease (Starr et al., 2008; but see Tang et al., 2005), Tourette syndrome (Zhuang et al., 2009) and dystonia (Lenz et al., 1998; Vitek et al., 1999; Vitek, 2002; Zhuang et al., 2004; Starr et al., 2005). The abnormally low frequency activity of GPi neurons is also induced in response to cortical microstimulation in dystonia mice (Chiken et al., 2008). These results suggest that tonic inhibitory signals from the GPi are critical to suppress abnormal involuntary movements. However, this simple hypothesis cannot explain the therapeutic effects of lesions in the GPi (pallidotomy) for hyperkinetic disorders (Lozano et al., 1997; Ondo et al., 1998; Okun & Vitek, 2004; Zhuang et al., 2009) or the fact that reversible inactivation of the GPi by the microinjection of muscimol, a GABA A receptor agonist, does not induce hyperkinetic movements in behaving monkeys (Inase et al., 1996; Desmurget & Turner, 2008). This important discrepancy has not yet been resolved.

In contrast with the GPi, the relationship between neural activity in the SNr and behavior could be understood more intuitively. The tonic activity of SNr neurons decreases during orofacial dyskinesia induced by systemic administration of apomorphine, a non-selective dopamine receptor agonist, in non-parkinsonian monkeys (Nevet et al., 2004). In line with this, clinical studies have shown that inappropriate saccades (direction errors during the antisaccade paradigm and/or timing errors during the visual/memory delay saccade paradigm, see Fig. 1) are generated more frequently in patients with Huntington’s disease (Lasker & Zee, 1997; Ali et al., 2006; Peltsh et al., 2008), tardive dyskinesia (Thaker et al., 1989; Cassady et al., 1992) and Tourette syndrome (LeVasseur et al., 2001). Furthermore, it has been shown clearly that SNr inactivation by muscimol microinjection induces impulsive saccades toward the contralateral direction in behaving monkeys (Hikosaka & Wurtz, 1985a). However, the inactivation of the SNr by muscimol microinjections does not reproduce completely the pattern of saccade deficits in patients with hyperkinetic disorders because SNr inactivation facilitates saccade initiation in behaving monkeys (Hikosaka & Wurtz, 1985a), whereas patients with hyperkinetic disorders have difficulties in initiating saccades required for appropriate task performance (Thaker et al., 1989; Lasker & Zee, 1997; LeVasseur et al., 2001; Mostofsky et al., 2001; Ali et al., 2006; Peltsh et al., 2008). To account for this saccade deficit, it might be necessary to take into account factors other than just the tonic firing rates of SNr neurons. For instance, degeneration of neurons in the CN giving rise to the direct pathway (CN D1 in Fig. 3) occurs in Huntington’s disease with the progression of the disease (Storey & Beal, 1993). Such a mechanism would attenuate the phasic inhibitory influence of the CN on the activity of SNr neurons, which might explain the difficulty of saccade initiation in patients with Huntington’s disease (Lasker & Zee, 1997; Winograd-Gurvich et al., 2003; Ali et al., 2006; Blekher et al., 2006; Peltsh et al., 2008). Further research is required to clarify this issue.

**Deep brain stimulation**

Although the SNr is not usually a target for DBS, it has been suggested that SNr DBS can potentially be used for axial symptoms in Parkinson’s disease (Chastan et al., 2009) and epilepsy (Loddenkemper et al., 2001; Kahane & Depaulis, 2010). However, a case report has shown that SNr DBS induces transient acute depression (Bejani et al., 1999). The mechanisms of these therapeutic and adverse effects of SNr DBS are still unclear. However, they might be inferred by delivering electrical microstimulation to the SNr and analyzing the resulting effects on saccades in behaving monkeys (Shires et al., 2010). A caveat of this strategy is that DBS and microstimulation might influence neural elements (e.g. cell bodies, synaptic terminals, passing fibers) around the electrode differently by unequal current density and spread (Ranck, 1975; Tehovnik, 1996; Butson & McIntyre, 2006; Carlson et al., 2010). Nevertheless, it is reasonable to assume that the effects of these techniques are similar at the network level because acute microstimulation during surgery induces similar therapeutic effects with chronic DBS (Limosin et al., 1998; Pollak et al., 2002; see also for DBS mechanisms – Liu et al., 2008; Deniau et al., 2010).

Microstimulation delivered to the SNr suppresses the activity of neurons in the SC in the same hemisphere as well as the opposite hemisphere at the same time during the visual delay saccade paradigm (Liu & Basso, 2008). This bilateral suppression is presumably mediated by the recruitment of SNr neurons projecting to the SC in the same and opposite hemispheres at the same time (Jiang et al., 2003; Cebrian et al., 2005). Although this suppression effect on the activity of SC neurons is straightforward, it is quite difficult to interpret the effects of the same microstimulation on saccade behavior (Basso & Liu, 2007; Liu & Basso, 2008). Based on the effect of SNr microstimulation on the activity of SC neurons (Liu & Basso, 2008), it was expected that SNr microstimulation would suppress saccade initiation. However, the experimental results are not consistent with this prediction. For contralateral saccades during the visual delay saccade paradigm, SNr microstimulation facilitates saccade initiation, whereas its effects on ipsilateral saccades are not consistent (Basso & Liu, 2007; Liu & Basso, 2008). During the memory delay saccade paradigm, SNr microstimulation increases the frequency of saccades with short and long reaction times at the same time, which causes a wider distribution of reaction times (Basso & Liu, 2007). Although this effect is not straightforward to interpret, it is partially similar to the abnormal saccade performance observed in patients with Parkinson’s disease who show a wider distribution of reaction times during the prosaccade paradigm (Chan et al., 2005) (abnormally variable performance has also been reported during other behavioral paradigms in patients with Parkinson’s disease) (Sheridan & Flowers, 1990; Burton et al., 2006; de Frias et al., 2007; Camicioni et al., 2008). During the visual delay saccade paradigm, the same patients with Parkinson’s disease also show a wider distribution of reaction times because they generate timing error saccades frequently before the instruction of saccade initiation (fixation point disappearance) is
The similarity between abnormal saccade behavior in monkeys with SNr microstimulation (Basso & Liu, 2007; Liu & Basso, 2008) and that in patients with Parkinson’s disease (Chan et al., 2005) might imply that the activity of SNr neurons in patients with Parkinson’s disease is enhanced inappropriately during the saccade paradigm. This idea is not consistent with a previous report in which the spontaneous firing rates of SNr neurons are unchanged in behaving parkinsonian monkeys, in which pathology was induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (Wichmann et al., 1999). However, it is still possible that the activity of SNr neurons during eye fixation before saccade initiation might be enhanced abnormally in patients with Parkinson’s disease because of the following two findings. First, a subset of neurons in the STN (STN in Fig. 3) increase activity during eye fixation (Matsunura et al., 1992). Second, glutamatergic signals sent from the STN to the SNr are enhanced in a rat model of Parkinson’s disease (Degos et al., 2005). Even if this idea is valid, it is still unclear how it explains the wider distribution of reaction times in patients with Parkinson’s disease. To clarify this issue, it might be necessary to take into account other factors, such as abnormal oscillatory activity in parkinsonian BG (Wichmann et al., 1999; Bevan et al., 2002; Brown, 2003; Rivlin-Etzion et al., 2006) and SNr projections to inhibitory neurons in the SC and thalamus (Pare et al., 1990; Kaneda et al., 2008).

Caudate nucleus

**Basic characteristics**

The CN is the oculomotor part of the striatum that receives input from virtually all cortical areas and the thalamus and sends GABAergic projections to downstream structures (Fig. 3) (Smith et al., 1998; Hikosaka et al., 2000; Nakano et al., 2000). The CN projection neurons are usually silent, but increase their activity phasically in relation to specific task events (Hikosaka et al., 1989a,b,c). The phasic activation of the CN projection neurons depends strongly on the amount of reward that monkeys can obtain after each correct saccade (Kawagoe et al., 1998; Lauwereyns et al., 2002; Hikosaka et al., 2006). The CN projection neurons are traditionally divided into the following two types. First, roughly half of the CN neurons project directly to the SNr and suppress the tonic activity of SNr neurons, which in turn facilitates saccade initiation (direct pathway; CN D1 in Fig. 3) (Smith et al., 1998; Hikosaka et al., 2000; Nakano et al., 2000). Second, the remaining half of the CN projection neurons innervate the external segment of the globus pallidus (GPe) and therefore activate SNr neurons by attenuating the inhibitory influences of the GPe on the SNr as well as STN neurons sending glutamatergic projections to the SNr (indirect pathway; CN D2 in Fig. 3) (Parent & Hazrati, 1995; Smith et al., 1998; Sato et al., 2000a; Kita, 2007).

The seminal BG model emphasizes the role of dopamine innervation from the substantia nigra pars compacta to the CN to control a balance between the direct and indirect pathway (Albin et al., 1989; DeLong, 1990). CN neurons giving rise to the direct and indirect pathways express predominantly dopamine D1- and D2-like receptors, respectively (Surmeier et al., 1992, 1996; Le Moine & Bloch, 1995). The model assumes that dopamine depletion caused by Parkinson’s disease attenuates the activity of CN D1 neurons giving rise to the direct pathway, while, at the same time, the activity of CN D2 neurons giving rise to the indirect pathway is enhanced. This opposite action of dopamine depletion on D1 and D2 neurons in the CN should cause the dominance of the indirect pathway over the direct pathway. This should suppress saccade initiation by enhancing inhibitory output from the SNr. In contrast, excessive dopamine in the CN should cause the opposite effect (saccade facilitation). Although anatomical studies challenge this model by showing coexpression of dopamine D1- and D2-like receptors (Aizman et al., 2000) and crosstalk between the direct and indirect pathways (Kawaguchi et al., 1990; Parent et al., 1995; Wu et al., 2000; Levesque & Parent, 2005), recent studies have shown that selective activation of striatal neurons giving rise to the direct and indirect pathways induces behavioral changes consistent with the model, at least in rodents (Hikida et al., 2010; Kravitz et al., 2010).

**Neuroimaging**

Neuroimaging studies have shown the involvement of the CN in a variety of saccade paradigms (Sweeney et al., 1996; O’Driscoll et al., 2000; Scholz et al., 2000; Gagnon et al., 2002; Gerardin et al., 2003; Simo et al., 2005; Brown et al., 2006; Dyckman et al., 2007; Ettinger et al., 2008; Cameron et al., 2009). Furthermore, they have revealed functional and structural abnormalities in the CN of patients with neurological and psychiatric disorders (see below).

The activity of the CN is enhanced abnormally during prosaccades in patients with autism, whereas their saccade performance is relatively intact (Takarae et al., 2007). In patients with first-episode psychosis, the larger volume of the CN predicts longer reaction times and shorter amplitudes for antisaccades (Ettinger et al., 2004). In presymptomatic Huntington’s gene carriers, the reduction of cortical projections (presumably from the FEF) to the body of the CN detected by diffusion tensor imaging is correlated with the increased variability of reaction times for volitional saccades (Kloppel et al., 2008), which has been suggested as a biomarker of Huntington’s disease (Winograd-Gurvich et al., 2003; Bleker et al., 2006; Petsch et al., 2008).

When the pro- and antisaccade paradigms are interleaved, CN activation is stronger for antisaccades than prosaccades in normal subjects (Sweeney et al., 1996; Brown et al., 2006; Dyckman et al., 2007; Ettinger et al., 2008; Cameron et al., 2009). Such enhanced activation is not observed in the CN of patients with schizophrenia (Raemaekers et al., 2002) who have difficulties in performing the antisaccade paradigm (Fukushima et al., 1988; Brownstein et al., 1995; Wu et al., 2000). However, this result is not conclusive because direction errors were not excluded from the analysis. Such contamination could attenuate the average activity of the CN in schizophrenic patients more severely than control subjects because of their higher rates of direction errors. Another factor that might account for the hypoactivation of the CN is antipsychotic medications that are taken by schizophrenic patients (Keedy et al., 2009). However, abnormal hypoactivation in the CN has also been reported in unaffected relatives of schizophrenic patients, whereas their antisaccade performance is relatively intact (Raemaekers et al., 2006).

We have recently revealed neural mechanisms underlying the selective involvement of the CN in antisaccade control by neurophysiological experiments in behaving monkeys (Watanabe & Munoz, 2009, 2010b; see also Ford & Everling, 2009). We found that a subset of putative projection neurons in the CN presumably controlling volitional saccades (hereafter, volitional neurons) have activity enhanced before antisaccade initiation compared with prosaccades (Fig. 4C–F) (Watanabe & Munoz, 2009). This does not necessarily mean that the CN only controls volitional saccades; we also identified a different subset of putative projection neurons in the CN presumably...
facilitating automatic direction error saccades (hereafter, automatic neurons; Fig. 4A and B) (Watanabe & Munoz, 2009). Automatic neurons have activity predominantly for saccades toward a contralateral stimulus (Fig. 4A and B). They increase activity on ipsilateral antisaccade trials (Fig. 4B) because they respond to the appearance of a visual stimulus on the contralateral hemifield. Interestingly, there are two types of volitional neurons with contralateral (Fig. 4C and D) and ipsilateral (Fig. 4E and F) saccade direction preferences, respectively. Based on the difference of saccade direction preferences between the population of automatic and volitional neurons, we propose the following hypothesis for antisaccade control (Fig. 5). Automatic neurons facilitate a direction error saccade toward a peripheral visual stimulus via the direct pathway. Simultaneously, contralateral saccade-preferred volitional neurons facilitate a correct antisaccade toward the opposite direction of the stimulus via the direct pathway. The conflict between opposite saccade commands issued by automatic neurons and contralateral saccade-preferred volitional neurons is resolved by ipsilateral saccade-preferred volitional neurons that suppress the direction error saccade command issued by automatic neurons through the indirect pathway (Watanabe & Munoz, 2009).

In addition to activity preceding saccade initiation, we have also identified the selective involvement of the CN in antisaccade preparation (Watanabe & Munoz, 2010b). Both automatic and volitional neurons have preparatory activity that predicts the reaction times of upcoming saccades even before visual stimulus appearance. The preparatory activity depends on the time elapsed from fixation initiation and the state of fixation (existence or absence of a central fixation point). Furthermore, the preparatory activity of volitional neurons is enhanced when antisaccade instruction is given before visual stimulus appearance. Such enhancement is absent when monkeys generate direction error saccades instead of correct antisaccades. In contrast, the preparatory activity of automatic neurons is not enhanced by antisaccade instruction or dependent on antisaccade performance. The selective enhancement of preparatory activity is observed in volitional neurons regardless of their saccade direction preferences. Therefore, we suggest that the enhanced preparatory activity of volitional neurons for antisaccades reflects the following two processes: preparation of saccade initiation and proactive suppression of inappropriate automatic saccades.

The combination of the evaluation of saccade behavior and functional/structural neuroimaging techniques in humans has a significant potential to establish how the CN as well as other brain structures influence abnormal saccade behavior in patients with neurological and psychiatric disorders. However, neurophysiological studies in behaving monkeys can decompose neuroimaging signals with the spatiotemporal resolution of single neuron/spike level. Therefore, it is obvious that great insights into the neural mechanisms underlying neurological and psychiatric disorders can be obtained by performing neurophysiological experiments in monkey models of clinical disorders. Such an approach has been taken to understand
abnormal saccade behavior in patients with Parkinson’s disease (see below).

**Dopamine depletion**

Based on the original model of the BG (Albin et al., 1989; DeLong, 1990), it is expected that saccade deficits in patients with Parkinson’s disease are caused mainly by dopamine depletion in the CN. However, because a subset of dopaminergic neurons projecting to the prefrontal cortex also die in patients with Parkinson’s disease (Javoy-Agid & Agid, 1980; Scotton et al., 1983; Mitchell et al., 1985), it is difficult to determine the specific influences of CN dopamine depletion on behavior only by analyzing saccade behavior in patients with Parkinson’s disease (Crevits & De Ridder, 1997; Briand et al., 1999; Chan et al., 2005; Gurvich et al., 2007; Cameron et al., 2010). This issue has been resolved clearly by behavioral analyses in monkeys with local dopamine depletion in the CN in one hemisphere (Kato et al., 1995; Kori et al., 1995). This manipulation induces less spontaneous saccades toward the contralateral side (Kato et al., 1995) and causes difficulties in generating contralateral memory-guided saccades (Kori et al., 1995). Interestingly, this manipulation does not influence visually guided saccades toward the contralateral direction, but increases timing error saccades toward a contralateral visual stimulus during the memory delay saccade paradigm (Kori et al., 1995). This is consistent with behavioral deficits observed in patients with Parkinson’s disease; they have a response bias toward automatic saccades programmed by external visual events rather than internally programmed volitional saccades (Briand et al., 1999; Chan et al., 2005; Cameron et al., 2010). This behavioral bias might explain the increased frequency of error saccades, triggered by abrupt visual stimulus appearance with very short reaction times (approximately 90–130 ms; Fischer & Weber, 1993), in patients with Parkinson’s disease (Chan et al., 2005; see also for more discussion – Watanabe et al., 2010).

Although local dopamine depletion in monkey CN causes saccade deficits similar to those observed in patients with Parkinson’s disease, it is still unclear how such saccade deficits are explained by BG neural circuits. For instance, the original BG model assumes dominant activation of CN neurons giving rise to the indirect pathway over those giving rise to the direct pathway in parkinsonian BG (Albin et al., 1989; DeLong, 1990). This predicts saccade suppression in general regardless of saccade paradigms. Therefore, it cannot explain the response biases toward visually driven saccades or the more frequent occurrence of express saccades in patients with Parkinson’s disease. Furthermore, the model does not account for neural activity observed in the CN of parkinsonian monkeys. Projection neurons in the CN are usually silent, but increase activity phasically in relation to specific task events (Hikosaka et al., 1989c). However, in parkinsonian monkeys, putative projection neurons are tonically active regardless of whether the tonic activity is enhanced or attenuated after systemic administration of levodopa (Li et al., 2008; see also Oye et al., 1970; Calabresi et al., 1993; Azdadi et al., 2009). It is possible that these biases may arise, at least in part, from compensatory mechanisms in the brain, as opposed to the direct result of dopamine depletion. In future studies, it will be important to address whether the enhanced activity of CN neurons explains the saccade behavior of patients with Parkinson’s disease.

**Deep brain stimulation**

Deep brain stimulation in the ventral CN and the core of the nucleus accumbens (a major input stage of the ventral BG) has been examined as a treatment for intractable obsessive-compulsive disorders and depression (Rauch et al., 2006; Lipsman et al., 2007; Aouizerate et al., 2009; Bewernick et al., 2010; Haynes & Mallet, 2010). However, the mechanisms underlying this treatment are still unknown. As described above, the BG form parallel loops, each of which is involved in different functions with similar architectures (Alexander et al., 1986; Nicola, 2007; Humphries & Prescott, 2010). Therefore, it would be beneficial to deliver electrical microstimulation in the dorsal CN where saccade-related neurons reside and analyze its effects on saccades to understand how CN DBS can influence BG neural circuits and behavior.

Microstimulation applied to the head/body of the CN evokes contralateral saccades in free-viewing cats (Kitama et al., 1991). We confirmed this observation in free-viewing monkeys (manuscript in preparation). This might be explained by the dominant activation of the direct pathway over the indirect pathway to disinhibit the SC in the same hemisphere. This predicts that microstimulation delivered to the CN during any saccade paradigm facilitates saccade initiation. However, we found the opposite effect in monkeys when they performed a randomly interleaved pro- and antisaccade paradigm (Watanabe & Munoz, 2010a; 2011). The major effects of CN microstimulation were the prolongation of reaction times regardless of saccade directions (contralateral or ipsilateral) or instructions (pro- or antisaccade). We also analyzed the effects of CN microstimulation on reaction times by the LATER model and found that CN microstimulation attenuates the rate of rise to the threshold for saccade initiation (Fig. 2B and C). This suppression effect was stronger for prosaccades compared with antisaccades when saccades were directed toward the contralateral direction. This asymmetric effect might indicate that saccade suppression signals issued from the CN might act on automatic saccade commands driven by the appearance of a visual stimulus more strongly than volitional saccade commands programmed for correct performance, as we hypothesized in Fig. 5 to resolve the conflict between automatic and volitional saccade commands for correct antisaccade performance.

The task-dependent effects of CN microstimulation on saccade initiation suggest that the effects of CN DBS might change dynamically depending on a wide variety of behavioral contexts in everyday life. These effects should be explored in more detail because they may also be exploited in different patient groups.

**Subthalamic nucleus**

**Basic characteristics**

The STN controls BG output signals directly by sending glutamatergic projections to the SNr and indirectly by activating neurons in the GPe, which then sends GABAergic projections to the SNr (Fig. 3) (Parent & Hazrati, 1995; Smith et al., 1998; Sato et al., 2000b). The STN receives feedback GABAergic input from the GPe (Parent & Hazrati, 1995; Smith et al., 1998; Sato et al., 2000a) and direct cortical glutamatergic input from the frontal cortex, including the FEF and supplementary eye field (Huerta et al., 1986; Stanton et al., 1988; Huerta & Kaas, 1990; Nambu et al., 2002). The disynaptic connection from the frontal cortex to the SNr via the STN is called the hyperdirect pathway because its conduction velocity is faster than other BG pathways (Nambu et al., 2000, 2002; Tachibana et al., 2008). A potential function of the hyperdirect pathway is to suppress actions immediately in response to some environmental changes by activating SNr neurons (Aron et al., 2007a,b; Isoda & Hikosaka, 2008). The STN is also a relay stage of the indirect pathway that originates from a subset of CN neurons (CN D2 in Fig. 3).
Saccade facilitation by deep brain stimulation

The STN has been a major target for DBS in patients with Parkinson’s disease (Benazzouz et al., 1993, 1996; Limousin et al., 1995, 1998; Lozano & Mahant, 2004; Perlmuter & Mink, 2006). STN DBS has also been examined in patients with dystonia (Chou et al., 2005; Kleiner-Fisman et al., 2007), epilepsy (Loddenkemper et al., 2001; Kahane & Depaulis, 2010) and obsessive-compulsive disorder (Mallet et al., 2008; Haynes & Mallet, 2010). It has been suggested that STN DBS ameliorates parkinsonian symptoms by blocking information flow through the STN and normalizing a balance between the direct and indirect/hyperdirect pathways (Degos et al., 2005). Furthermore, STN DBS also improves the irregularity of BG output signals in parkinsonian monkeys (Hashimoto et al., 2003). The effects of STN DBS on the activity of SNr neurons are presumably mediated by the direct activation of glutamatergic projections from the STN to the SNr as well as the indirect enhancement of inhibitory influences on the SNr through the STN–GPe–SNr pathway (Kita et al., 2005; Windels et al., 2005).

It has been shown that STN DBS influences saccade performance in patients with Parkinson’s disease (Rivaud-Pechoux et al., 2000; Sauleau et al., 2008; Temel et al., 2008, 2009; Wark et al., 2008; Fawcett et al., 2010; Yugeta et al., 2010). STN DBS shortens reaction time and increases saccade amplitude during the prosaccade, antisaccade and memory delay saccade paradigms (Sauleau et al., 2008; Temel et al., 2008, 2009; Fawcett et al., 2010; Yugeta et al., 2010). The effects of STN DBS on reaction times have been analyzed by the LATER model (Fig. 2; Temel et al., 2008, 2009). The model indicates that STN DBS shortens reaction times by increasing the rate of rise to the threshold for saccade initiation during the prosaccade paradigm. This could be attributed to several possibilities. First, STN DBS could reduce the inhibitory influences on the SC and the FEF from the SNr. The reduction of the activity of SNr neurons could be mediated by the activation of the STN–GPe–SNr pathway, or by blocking saccade suppression signals carried by BG pathways going through the STN (hyperdirect and indirect pathways). Second, STN DBS could include the spread of electrical current to the internal capsule, leading to activation of axons projecting from the FEF to the SC (Wichmann et al., 1994; Shields et al., 2007). Third, STN DBS could activate SC neurons projecting to the STN antidromically (Tokuno et al., 1994; Coizet et al., 2009). Further research is required to establish the precise mechanisms of saccade facilitation by STN DBS.

Saccade impulsivity by deep brain stimulation?

Recent studies have shown that one of the side-effects produced by STN DBS is the induction of impulsive behavior (Frank et al., 2007; Ballanger et al., 2009; Halbig et al., 2009; Hershey et al., 2010; Wylie et al., 2010). However, this view is not supported fully by studies analyzing saccade performance. If STN DBS enhances impulsivity, patients should generate more direction error saccades toward the stimulus during the antisaccade paradigm (Fig. 1B) when DBS is present compared with when DBS is absent. However, such an effect was not observed (Rivaud-Pechoux et al., 2000; Yugeta et al., 2010). This negative finding might be explained by the following three possibilities. First, saccade impulsivity might be detected by focusing only on trials in which saccades are triggered with short reaction times (Wylie et al., 2010) because direction error saccades are observed mainly in the distribution of short reaction times (Fischer & Weber, 1992; Bell et al., 2000; Dafoe et al., 2007). The previous studies might have failed to detect saccade impulsivity during the antisaccade paradigm because they focused only on the average frequency of direction error saccades regardless of their reaction times (Rivaud-Pechoux et al., 2000; Yugeta et al., 2010). Second, saccade impulsivity might be induced by DBS in the ventral STN, but not in the dorsal STN (Hershey et al., 2010). This idea is supported further by the fact that saccade-related neurons are clustered in the ventral STN (Matsumura et al., 1992; Fawcett et al., 2005a). In contrast, parkinsonian motor symptoms are ameliorated best by DBS in the dorsal STN (Lanotte et al., 2002; Starr et al., 2002; Voges et al., 2002), which is consistent with the locations of neurons related to skeletal movements (Wichmann et al., 1994). Therefore, it is critical to identify stimulation sites accurately in the STN to interpret experimental results (see also Rodriguez-Oroz et al., 2010). Third, medication (levodopa) taken by patients in the previous studies might have masked the effects of STN DBS on the frequency of direction error saccades because levodopa delays the initiation of saccades toward visual stimuli (Michell et al., 2006; Hood et al., 2007; but see Hotson et al., 1986; Temel et al., 2009) and decreases the frequency of direction error saccades during the antisaccade paradigm (Hood et al., 2007; see also for the effects of STN DBS on saccades without medication – Fawcett et al., 2010).

Saccade impulsivity can also be evaluated by the memory delay saccade paradigm. Patients with Parkinson’s disease often fail to suppress timing error saccades in response to the flash of a peripheral visual stimulus (Crevits & De Ridder, 1997; Chan et al., 2005; Gurvich et al., 2007). If STN DBS enhances saccade impulsivity, the occurrence of such timing error saccades should increase. However, one experimental result does not support this; STN DBS decreased the frequency of timing error saccades (Yugeta et al., 2010). Improved inhibitory control by STN DBS has also been reported using a countermanding paradigm with manual responses (van den Wildenberg et al., 2006). The beneficial effect of STN DBS on saccade inhibition during the memory delay saccade paradigm is difficult to interpret based on the hypothesis of saccade impulsivity induced by STN DBS, especially with the potential confounding factors described above (dorsal vs. ventral stimulation sites and on vs. off medication). A potential account for this phenomenon is that STN DBS enhances eye fixation signals carried by a subset of STN neurons (Matsumura et al., 1992). This idea is consistent with a case report in which STN DBS improves fixation stabilities in a patient with Parkinson’s disease (Wark et al., 2008). Even if this is true, it is still unclear how STN DBS could improve the ability of eye fixation and saccade initiation at the same time because it has been suggested that neural circuits controlling eye fixation and saccade initiation have competitive inhibitory interactions between them (Munoz & Wurtz, 1993a,b; Hanes et al., 1998; Munoz & Fecteau, 2002; Pare & Hanes, 2003).

External segment of the globus pallidus

Basic characteristics

The GPe sends GABAergic projections to all three BG nuclei reviewed above (SNr, CN and STN) (Parent & Hazrati, 1995; Smith et al., 1998; Sato et al., 2000a; Kita, 2007). The activity of GPe neurons is controlled by GABAergic input from CN neurons giving rise to the indirect pathway and glutamatergic input from the STN (Fig. 3) (Parent & Hazrati, 1995; Smith et al., 1998; Sato et al., 2000a; Kita, 2007). Although the activity of GPe neurons during saccade paradigms has been reported recently (Yoshida & Tanaka, 2009; Shin & Sommer, 2010), their functional role in saccade control...
is still unclear. Functional neuroimaging studies have also shown the activation of the globus pallidus during several saccade paradigms (Petit et al., 1993; Gagnon et al., 2002; Simo et al., 2005; see also Matsuda et al., 2004; Tu et al., 2006). However, it is unclear whether the activation is derived from the GPe or the GPi because of the limited spatial resolution of the neuroimaging techniques that were employed.

**Pharmacological manipulation**

Acute GPe DBS ameliorates hypokinesia (decreased bodily movements), but could induce hyperkinetic movements in patients with Parkinson’s disease (Yelnik et al., 2000; Vitek et al., 2004; Payoux et al., 2009). Hyperkinetic movements induced by acute GPe DBS have also been reported in patients with dystonia (Mouton et al., 2006). These clinical findings are consistent with the fact that hyperkinetic movements are induced by the selective activation of neurons in the sensorimotor part of the GPe with microinjection of bicuculline, a GABA<sub>A</sub> receptor antagonist, in behaving monkeys (Crossman et al., 1984, 1988; Matsumura et al., 1995; Inase et al., 1996; Grabli et al., 2004). Interestingly, a recent study has shown that bicuculline microinjection into the limbic part of the GPe induces stereotypy, whereas the same manipulation in the association part of the GPe causes attention deficit and/or hyperactivity (Grabli et al., 2004). These behavioral deficits in monkeys expressed in skeletal movements are similar to those in patients with Tourette’s syndrome, attention deficit/hyperactivity disorder and obsessive-compulsive disorder. However, it is unknown whether bicuculline microinjection into the limbic and association parts of the GPe in behaving monkeys causes the saccade deficits observed in patients with these disorders. For instance, patients with Tourette’s syndrome have longer reaction times during the pro- and antisaccade paradigms (LeVasseur et al., 2001; Mostofsky et al., 2001) and higher rates of timing error saccades during the visual and memory delay saccade paradigm (LeVasseur et al., 2001). Patients with attention deficit/hyperactivity disorder generate more direction error saccades during the antisaccade paradigm and generate more express saccades triggered with very short reaction times during the prosaccade paradigm (Munoz et al., 2003). Patients with obsessive-compulsive disorder have longer reaction times during the antisaccade paradigm (van der Wee et al., 2006).

A recent study has shown that reversible inactivation of the GPe by muscimol microinjections has significant impacts on behavioral performance during the pro- and antisaccade paradigm in monkeys (Yoshida & Tanaka, 2009). Although it is difficult to explain the observed saccade deficits because of the small number of microinjection sites, this clearly indicates that the GPe is a critical structure for saccade control.

**Extended saccade control circuit in the basal ganglia**

We have described the recent advances of experimental research for the BG nuclei included in the traditional saccade control circuit in the BG (Hikosaka et al., 2000; Fig. 3). However, accumulating evidence from clinical and neuroimaging studies in humans and neurophysiological studies in behaving monkeys suggests the potential involvement of other BG nuclei in saccade control. Here, we extend the traditional BG model for saccade control (Fig. 6), and describe the potential functions of the putamen, GPi, pedunculopontine tegmental nucleus (PPN), and thalamus for saccade control.

**Putamen**

**Basic characteristics**

The putamen is another part of the striatum that has been thought to control skeletal movements (Alexander & Crutcher, 1990; Mink, 1996; Fig. 6). However, the putamen might also be involved in saccade control because it receives input from the FEF (Stanton et al., 1988; Parthasarathy et al., 1992; Cui et al., 2003) and sends its projections to the SNr (Parent & Hazrati, 1994). It is also possible that projections from the putamen to the GPi are involved in saccade control (see Internal segment of the globus pallidus).

**Neuroimaging**

Functional neuroimaging studies have repeatedly shown the involvement of the putamen in a variety of saccade paradigms (Petit et al., 1993, 1996; O’Driscoll et al., 1995; O’Sullivan et al., 1995; Sweeney et al., 1996; Dejardin et al., 1998; Gagnon et al., 2002; Gerardin et al., 2003; Simo et al., 2005; Dyckman et al., 2007). The findings are very similar to what we have described in the CN. During the pro- and antisaccade paradigm, the activity of the putamen is higher for antisaccades compared with prosaccades (O’Driscoll et al., 1995; Sweeney et al., 1996; Dyckman et al., 2007; see also Matsuda et al., 2004). In patients with schizophrenia, such enhanced putaminal activity is not observed for antisaccades (Raemaekers et al., 2002; see also Tu et al., 2006) and memory delay saccades (Camchong et al., 2006), although the analyses did not exclude direction and timing errors.

A potential functional difference between the putamen and CN has been suggested using a saccade paradigm that dissociates the temporal and spatial predictability of the peripheral visual stimuli that the subjects are required to look at (Gagnon et al., 2002). The activity of the putamen is enhanced when the temporal timing of the stimuli is predictable. In contrast, the activity of the CN is enhanced when the spatial location of the stimuli is predictable. This fits nicely with a popular conceptual model of saccade control based on psychophysical...
studies in which there are two separate mechanisms controlling when and where to initiate saccades (Findlay & Walker, 1999). However, the results of our recent neurophysiological study in behaving monkeys do not agree with this strict dissociation between the temporal and spatial control of saccades by the putamen and CN; saccade-related neurons in the CN issue temporal signals before the appearance of a peripheral visual stimulus and spatial signals after stimulus appearance (Watanabe & Munoz, 2009, 2010b). Further research is obviously required to clarify this issue, as far as we know, there has been no neurophysiological study in the putamen for saccade control in behaving monkeys. The hypothesis that the putamen and CN control when and where to initiate saccades, respectively, would be an interesting working hypothesis to facilitate future research.

Internal segment of the globus pallidus

Basic characteristics

The GPi is the other main output structure of the BG that has been examined mainly for skeletal movements (Alexander & Crutcher, 1990; Mink, 1996; Fig. 6). However, recent studies in behaving monkeys have shown the existence of GPi neurons modulating their activity in relation to saccades (Yoshida & Tanaka, 2009; Shin & Sommer, 2010). This suggests that the GPi might also be involved in saccade control. Indeed, this hypothesis is consistent with the following clinical studies.

Pallidotomy

Lesions in the GPi (pallidotomy) have been used for alleviating the motor symptoms of BG disorders, such as Parkinson’s disease (Laitinen et al., 1992; Dogali et al., 1995; Lozano et al., 1995; Baron et al., 1996; Okun & Vitek, 2004), dystonia (Lozano et al., 1997; Ono et al., 1998; Vitek et al., 1998; Okun & Vitek, 2004), Tourette syndrome (Zhuang et al., 2009), and tardive dyskinesia (Wang et al., 1997). The effects of unilateral pallidotomy on saccade control have been reported in patients with Parkinson’s disease (Averbuch-Heller et al., 1999; Blekher et al., 2000; O’ Sullivan et al., 2003). Pallidotomy leads to an increase in the frequency and amplitude of small, inappropriate saccades (square-wave jerks) that interrupt steady fixation upon a stationary visual stimulus (Averbuch-Heller et al., 1999; O’Sullivan et al., 2003). The small inappropriate saccades after unilateral pallidotomy are directed equally toward the contralateral and ipsilateral directions with respect to the lesion side. These findings raise the possibility that the GPi participates in the control of eye fixation. This predicts the facilitation of saccade initiation by pallidotomy because it has been suggested that neural circuits controlling eye fixation have inhibitory influences on those triggering saccades (Munoz & Wurtz, 1993a,b; Hanes et al., 1998; Munoz & Fecteau, 2002; Pare & Hanes, 2003). However, pallidotomy does not influence saccade initiation during the prosaccade, antisaccade and memory delay saccade paradigms (Blekher et al., 2000; O’Sullivan et al., 2003). Pallidotomy decreases the peak velocities of internally driven saccades, including antisaccades and memory delay saccades (Blekher et al., 2000).

Deep brain stimulation

Deep brain stimulation in the GPi has been used for Parkinson’s disease (Siegfried & Lippitz, 1994; Boraud et al., 1996; Gross et al., 1997; Lozano & Mahant, 2004; Perlmutter & Mink, 2006) and dystonia (Hamani & Moro, 2007; Krauss, 2010; Welter et al., 2010). Furthermore, the effect of this treatment has been examined in several patients with Tourette syndrome (Hamani & Moro, 2007; Hariz & Robertson, 2010; Welter et al., 2010) and Huntington’s disease (Moro et al., 2004; Hebb et al., 2006; Biolsi et al., 2008; Fasano et al., 2008). The effects of GPi DBS on saccades have been reported in a single patient with Parkinson’s disease (Straube et al., 1998) and another single patient with Huntington’s disease (Fawcett et al., 2005b). However, results are not consistent between these studies. In a patient with Parkinson’s disease (Straube et al., 1998), GPi DBS improved antisaccade performance by facilitating the initiation of correct antisaccades toward the opposite location of a peripheral visual stimulus and decreasing the frequency of direction error saccades toward the stimulus. This manipulation also increased the amplitude of saccades during the memory delay saccade paradigm, whereas the reaction times and amplitudes of prosaccades were not affected. However, in a patient with Huntington’s disease (Fawcett et al., 2005b), GPi DBS improved prosaccades (shortened reaction time, increased amplitude, increased velocity), whereas the control of saccades deteriorated during the memory delay saccade paradigm (prolonged reaction time, decreased amplitude). More studies are warranted to establish the effects of GPi DBS on saccade control.

The above results from clinical studies with pallidotomy and DBS suggest that the GPi is involved in saccade control. However, it is also possible that these treatments applied to the GPi influence passing fibers from structures included in the traditional saccade control system. In future research, it will be critical to examine whether saccades are influenced by selective activation/inactivation of cell bodies in the GPi. This can be achieved, for instance, by GABA_A receptor agonist/antagonist (muscimol/bicuculline) microinjections that affect cell bodies and not axons of passage.

Pedunculopontine tegmental nucleus

Basic characteristics

The PPN has been suggested recently as another BG nucleus because of its tight anatomical interconnections with traditional BG nuclei (Mena-Segovia et al., 2004; Fig. 6). The PPN receives important GABAergic input from the GPi and SNr, and glutamatergic input from the STN, cerebral cortex including the FEF and deep cerebeller nuclei (Pahapill & Lozano, 2000; Mena-Segovia et al., 2004; Matsumura, 2005; Winn, 2006; Jenkinson et al., 2009). The PPN has descending projections to the brainstem and spinal cord, and it also has more extensive widespread ascending projections to virtually all BG nuclei, the thalamus, cerebral cortex and SC (Lavoie & Parent, 1994; Pahapill & Lozano, 2000; Mena-Segovia et al., 2004; Matsumura, 2005; Winn, 2006; Jenkinson et al., 2009). The involvement of the PPN in saccade control can be expected from its widespread ascending projections.

Deep brain stimulation

The PPN has been examined recently as another potential target of DBS for the treatment of freezing of postural instability and gait disorders in Parkinson’s disease and progressive supranuclear palsy that cannot be treated effectively by DBS in other BG nuclei (Mazzone et al., 2005; Plaha & Gill, 2005; Stefani et al., 2007; Ferraye et al., 2010; Moro et al., 2010). The anatomical characteristics of the PPN described above predict that PPN DBS influences not only gait and posture by activating the descending projections but also other motor and non-motor (e.g. working memory) functions by activating the ascending projections (Lim et al., 2009; Alessandro et al., 2010; Thevathasan et al., 2010). Although the effects of PPN DBS on
saccades have not been reported, there is evidence from neurophysiological studies in behaving monkeys suggesting that the PPN is involved in saccade control.

A subset of PPN neurons increase or decrease their activity in response to task events during the prosaccade paradigm (Kobayashi et al., 2002; Okada & Kobayashi, 2009). PPN neurons also change activity depending on the performance of monkeys (Kobayashi et al., 2002). Separate populations of PPN neurons carry information regarding predicted and actual reward values, respectively, which are presumably sent to dopaminergic neurons in the substantia nigra pars compacta for the computation of reward prediction error (Okada et al., 2009). The PPN also sends cholinergic projections to the SC (Graybiel, 1978; Illing & Graybiel, 1985; Beninato & Spencer, 1986; Hall et al., 1989), which might facilitate saccade initiation because microinjections of the cholinergic agonist nicotine into the SC facilitate saccade initiation (Aizawa et al., 1999; Watanabe et al., 2005).

The above findings indicate the involvement of the PPN in saccade control. However, further research is required to clarify how the PPN controls saccades by its widespread ascending projections to the BG, thalamus, cerebral cortex and SC. The analyses of saccade behavior in patients with PPN DBS might shed light on this issue, although it is highly likely that PPN DBS also influences structures surrounding the PPN directly (Alam et al., 2011).

**Thalamus**

**Basic characteristics**

We describe the involvement of the thalamus in saccade control here because it receives input not only from the SNr and SC, but also from the GPi and PPN (Fig. 6), although these subcortical structures do not send projections to individual thalamic nuclei equally (Ruschen et al., 1987; Lavoie & Parent, 1994; Lynch et al., 1994; Sakai et al., 1996; Sidibe et al., 1997, 2002; Erickson & Lewis, 2004; Erickson et al., 2004; Sommer & Wurtz, 2004; Tanibuchi et al., 2009). The thalamus is included in the traditional cortex–BG circuit as a simple relay station (Alexander & Crutcher, 1990; Mink, 1996; Hikosaka et al., 2000). This view has been updated significantly based on recent anatomical studies (Haber & McFarland, 2001; Smith et al., 2004). Individual thalamic nuclei and functionally related cortical areas form reciprocal connections with each other and project to common functional subdivisions within the striatum (Sadikot et al., 1992a,b; Gimenez-Amaya et al., 1995; Sidibe & Smith, 1996; McFarland & Haber, 2000, 2001, 2002; Sidibe et al., 2002).

Neurophysiological studies in behaving monkeys have shown a variety of signals during saccade paradigms in the central thalamus including the mediodorsal nucleus, internal medullary lamina, and ventral anterior (VA)/ventral lateral (VL) nuclei (Schlag & Schlag-Rey, 1984; Schlag-Rey & Schlag, 1984; Tanibuchi & Goldman-Rakic, 2003; Wyder et al., 2003; Sommer & Wurtz, 2004; Watanabe & Funahashi, 2004; Kunimatsu & Tanaka, 2010). A potential function of the central thalamus is to carry corollary discharge from the SC to the cerebral cortex (Gaymard et al., 1994; Sommer & Wurtz, 2002; Bellebaum et al., 2005). However, this does not necessarily mean that the central thalamus is not involved in triggering saccades (see below).

**Neuroimaging**

Results derived from functional neuroimaging in the thalamus are very similar to those reported in the CN and putamen (Petit et al., 1993; Anderson et al., 1994; O’Driscoll et al., 1995; O’ Sullivan et al., 1995; Sweeney et al., 1996; Simo et al., 2005; Dyckman et al., 2007; Ettinger et al., 2008). During the pro- and antisaccade paradigm, the thalamus shows stronger activity for antisaccades compared with prosaccades (O’Driscoll et al., 1995; Matsuda et al., 2004; Dyckman et al., 2007). Such enhanced thalamic activity is not observed in patients with schizophrenia (Tu et al., 2006; Fukumoto-Motshita et al., 2009; see also Camchong et al., 2006), although direction errors were not excluded from the analysis. The attenuation of the thalamic activity during antisaccades might be related to the smaller volume of the thalamus relative to brain size in schizophrenic patients (Byrne et al., 2009).

The importance of the thalamus for correct antisaccade performance is supported further by a recent neurophysiological study in monkeys (Kunimatsu & Tanaka, 2010). Neurons in the VA/VL nuclei have enhanced activity for antisaccades compared with prosaccades. Furthermore, artificial inactivation of these thalamic neurons by muscimol microinjections increases direction error saccades and prolongs the reaction times of antisaccades, whereas they do not influence prosaccades.

The consistent results from the neuroimaging and neurophysiological studies suggest that the enhanced activation in human thalamus during antisaccades might originate from the VA/VL nuclei. This is supported further by the fact that neurons in the mediodorsal nucleus thalamus have activity equal for pro- and antisaccades as a whole and their inactivation by muscimol microinjections does not influence antisaccade performance (Kunimatsu & Tanaka, 2010). The latter finding seems odd because the mediodorsal nucleus has strong reciprocal connections with the dorsolateral prefrontal cortex (Ruschen et al., 1987; McFarland & Haber, 2002; Tanibuchi et al., 2009) and inactivation/lesions of the dorsolateral prefrontal cortex impair antisaccade performance (Guitton et al., 1985; Pierrot-Deseiligny et al., 2003; Ploner et al., 2005; Condy et al., 2007; see also Cameron & Watanabe, 2010). Further research is required to clarify this point.

**Deep brain stimulation**

Deep brain stimulation has been applied to multiple thalamic nuclei for the treatment of a variety of neurological and psychiatric disorders. The ventral intermediate nucleus (Vim), corresponding to the posteroventral part of the VL nuclei and receiving major input from the cerebellum (Macchi & Jones, 1997), has been targeted for tremor in Parkinson’s disease, essential tremor and multiple sclerosis (Benabid et al., 1991, 1996; Limousin et al., 1999; Torres et al., 2010). The ventralis oralis anterior and ventralis oralis posterior nuclei, corresponding to the anterior VL nuclei and receiving major input from the GPi (Macchi & Jones, 1997), have been examined as other potential target for post-traumatic and multiple sclerosis tremor (Foo et al., 2006), focal hand dystonia (Fukaya et al., 2007; Goto et al., 2008), and postanoxic dystonia with damaged GPi (Ghika et al., 2002; Constantoyannis et al., 2009; Katsakori et al., 2009). The therapeutic effects of thalamic DBS are presumably achieved by disrupting neural activity correlated with abnormal involuntary movements (Lenz et al., 1988, 1994, 1999, 2002; Hua et al., 1998; Guehl et al., 2003; Brodkey et al., 2004; Molnar et al., 2005). Because Vim and ventralis oralis anterior/ventralis oralis posterior are adjacent structures, it is reasonable to speculate that electric current delivered to one of these nuclei probably spreads to the other nucleus. Furthermore, because projections from the GPi and cerebellar nuclei are not segregated strictly in the Vim and ventralis oralis anterior/ventralis oralis posterior (Sakai et al., 1996), DBS in these
thalamo-cerebellar networks.

Effects of Vim DBS on prosaccades have been reported for patients with essential tremor (Kronenbuerger et al., 2010) and tremor-dominant Parkinson’s disease (Temel et al., 2009). These studies have shown that Vim DBS does not influence reaction times (Temel et al., 2009; Kronenbuerger et al., 2010), whereas contralateral saccades become hypometric (Kronenbuerger et al., 2010). The hypometric saccades induced by Vim DBS might be explained by the disruption of the cortex–cerebellum network because the cerebellum is involved in the control of saccade amplitude (Robinson & Fuchs, 2001; see also Briggel et al., 1984; Hirose et al., 1985; Gaymard et al., 2001). However, this does not necessarily mean that the BG do not contribute to this phenomenon because electrical stimulation in multiple BG nuclei influences saccade amplitude (Straube et al., 1998; Fawcett et al., 2005b, 2010; Basso & Liu, 2007; Sauleau et al., 2008; Watanabe & Munoz, 2010a; Yugeta et al., 2010).

Deep brain stimulation has also been applied to other thalamic nuclei. For example, DBS has been applied to the centromedian-parafascicular complex (CM/Pf) for Tourette syndrome (Vandewalle et al., 1999; Visser-Vandewalle et al., 2003; Houeto et al., 2005; Servello et al., 2008; Porta et al., 2009) and Parkinson’s disease (Caparros-Lefebvre et al., 1999; Mazzone et al., 2006; Peppe et al., 2008; Jouve et al., 2010). Although the effects of CM/Pf DBS on saccades have not been reported, it is possible that CM/Pf DBS also influences saccade deficits observed in patients with these disorders (Tourette: LeVasseur et al., 2001; Mostofsky et al., 2001; Parkinson’s disease: Crevits & De Ridder, 1997; Briand et al., 1999; Chan et al., 2005; Gurvich et al., 2007; Cameron et al., 2010).

Neurophysiological studies in behaving monkeys have shown that CM/Pf neurons respond to behaviorally salient sensory stimuli (Matsumoto et al., 2001; Minamimoto & Kimura, 2002). Inactivation of CM/Pf neurons by muscimol microinjections impairs the ability of monkeys to prepare for actions following behaviorally salient stimuli (Matsumoto et al., 2001; Minamimoto & Kimura, 2002). Electrical microstimulation applied to the CM prolongs the reaction times of reaching movements in response to visual stimulus appearance (Minamimoto et al., 2005). Based on these observations, we predict the following two effects of CM/Pf DBS on saccadic performance. First, CM/Pf DBS disrupts neural responses to behaviorally salient sensory stimuli. This might reduce direction errors during the antisaccade paradigm and timing errors during the visual/memory delay saccade paradigms. Second, CM/Pf DBS suppresses saccade initiation by activating afferents to the STN, SNr and GPe (Sadikot et al., 1992a; Moulouex et al., 1995).

Summary and future directions

In this review, we have summarized experimental results from neuroimaging and clinical studies in humans and tried to account for them based on the current knowledge of BG functions derived from neurophysiological studies in behaving monkeys by taking advantage of homologies in saccade behavior. In addition to significant updates made in the traditional BG saccade control circuit including the SNr, CN, STN and GPe, it has been emerging that the BG saccade control circuit should be extended to include other BG nuclei (putamen, GPe and PPN) and take into account interactions between the BG and thalamic nuclei. These conceptual advances for the BG mechanisms of saccade control will stimulate new clinical and basic studies in future. However, before moving forward, we should address the following four issues to interpret the experimental results that we have reviewed in this article.

First, the most popular method currently used to manipulate neural activity is electrical stimulation in both clinical patients (DBS) and behaving monkeys (microstimulation). Electrical stimulation is effective because its parameters can be manipulated very easily. However, it activates not only cell bodies but also fibers of passage around the tip of electrodes. The same issue is applied to lesions (e.g. pallidotomy). Therefore, it is unclear whether the observed effects of these techniques can be interpreted as the manipulation of neural activity in target structures. Therapeutic effects of DBS and lesions might be achieved by their influences on both cell bodies and axons of passage. However, to establish the functional role of each BG nucleus in saccade control, it will be critical to adopt techniques that manipulate the activity of cell bodies selectively, such as with microinjections of pharmacological agents and recently developed optogenetics (Gradinaru et al., 2009; Kravitz et al., 2010).

Second, the effects of the artificial manipulation of neural activity in each BG nucleus presumably depend on the network state of the BG. For instance, previous studies including ours have shown that the effects of CN microstimulation depend on saccade paradigms as well as the timings of current delivery (Kitama et al., 1991; Nakamura & Hikosaka, 2006; Watanabe & Munoz, 2010a; 2011). This suggests that artificial signals issued by CN microstimulation are modulated extensively by endogenous signals within the BG before influencing saccade behavior. This might also imply that the effects of DBS on saccades could change depending on the diseases that patients suffer from. For instance, the effects of GPI DBS on saccades are different between patients with Parkinson’s (Straube et al., 1998) and Huntington’s (Fawcett et al., 2005b) diseases. This discrepancy is not conclusive because both of these studies report the behavior of only one patient. However, the inconsistent results might reflect different network states induced by different diseases, which could influence artificial signals created by GPI DBS and resultant saccade behavior. This is supported further by the fact that subthalamicotomy (STN lesion) is an effective surgical treatment for Parkinson’s disease, whereas it could induce hemiballismus in normal BG (Guridi & Oleso, 2001). Therefore, we need to interpret data from patients with a specific BG disorder carefully before concluding the functional role of each BG nucleus in saccade control.

Third, most previous studies report only the averages of saccadic performance (e.g. reaction times, error rates). Such analyses could show whether saccadic performance is influenced by BG disorders and/or surgical interventions. However, it is very difficult to infer mechanisms underlying resultant saccade behavior based only on such limited analyses. Recent studies have combined electrical stimulation and behavioral analyses with simple cognitive models, such as the LATER model (Temel et al., 2008, 2009; Watanabe & Munoz, 2010a; 2011). This approach is more advantageous than just analyzing average reaction times because it gives us some insights about how electrical signals are transformed into saccade commands by analyzing the whole distributions of reaction times. Furthermore, to interpret direction errors during the antisaccade paradigm and timing errors during the visual/memory delay paradigm, more sophisticated analyses assuming competition between correct and error responses (Trappenberg et al., 2001; Boucher et al., 2007) will be valuable to identify deficits in the saccade decision process.

Fourth, the extension of the traditional BG saccade control circuit is an interesting direction for future research. Because the putamen and GPe have been examined mainly for skeletal movements, it is still unclear whether and how they contribute to saccade control. An interesting working hypothesis to address this issue is that the extended circuit (putamen and GPe) controls when to initiate a saccade, whereas the traditional circuit (CN and SNr) controls where
to direct a saccade (Gagnon et al., 2002) (Fig. 6). This view is consistent with the fact that saccade-related neurons in the GPs do not have clear saccade direction preferences (Yoshida & Tanaka, 2009) and unilateral pallidotomies increases small inappropriate saccades directed equally toward the contralateral and ipsilateral directions with respect to the lesion side (Averbuch-Heller et al., 1999; O’ Sullivan et al., 2003). This hypothesis is also in line with a popular conceptual model of saccade control based on psychophysical studies (Findlay & Walker, 1999). Interactions between the traditional and extended circuit might be achieved via the PPNE, although other possibilities are equally likely, such as interactions between the cortex–thalamus feedback loops (McFarland & Haber, 2002). These mechanisms might explain reaction time correlations during eye–hand coordination (Dean et al., 2011). However, evidence supporting the direct involvement of the extended circuit in saccade control is still weak. GPs DBS influences saccade performance (Straube et al., 1998; Fawcett et al., 2005b), although the results are inconsistent between the two studies based only on one patient; in addition, the influences of GPs DBS on passing fibers cannot be excluded. Controlled experiments in behaving monkeys, such as reversible inactivation of GPs neurons by muscimol microinjection, will be required to clarify this point.

In addition to the above issues, we believe that it will be critical to develop and use monkey models of BG disorders (Benazzouz et al., 1993; Kato et al., 1995; Kori et al., 1995; Boraud et al., 1996; Grabl et al., 2004) to establish solid linkage between saccade abnormalities observed in clinical patients and detailed neural circuits that can be explored only in monkeys. The integration of theoretical, clinical, neuroimaging, and neurophysiological research using the same saccade paradigms will allow us to develop a coherent framework for the modulatory role of the BG in saccade control. This will also give us some insights about how the BG influence functions controlled by other cortex–BG loops, such as emotion and cognition.

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Abbreviations

BG, basal ganglia; CM/Pf, centromedian-parafascicular complex; CN, caudate nucleus; DBS, deep brain stimulation; FEF, frontal eye field; GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; PPNE, pedunculopontine tegmental nucleus; SC, superior colliculus; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; Vim, ventral intermediate nucleus; VL, ventral lateral nucleus.

References


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