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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

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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

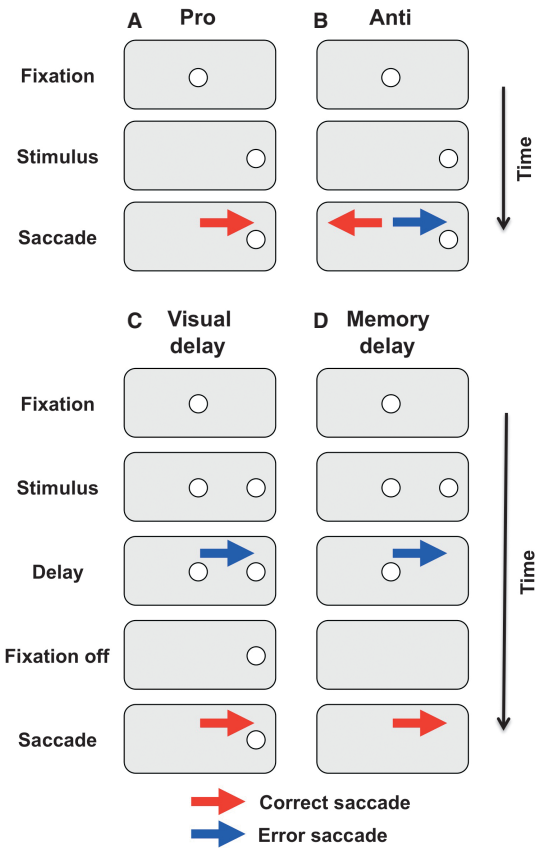

FIG. 1. Saccade paradigms. Prosaccade (A) and antisaccade (B) paradigms. After subjects fixate on the central fixation point, a stimulus appears. Subjects generate a saccade toward the stimulus (prosaccade) or toward the opposite of the stimulus (antisaccade). During the antisaccade paradigm, subjects 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).

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,

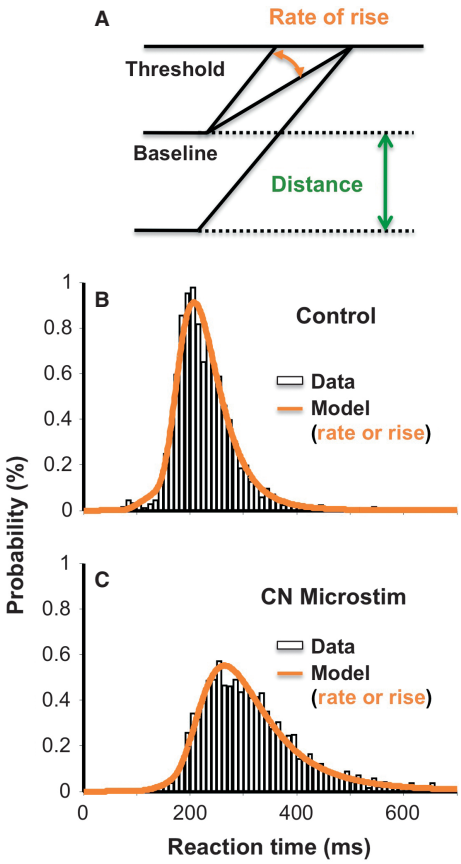

FIG. 2. An example of saccade models. (A) LATER model. The saccade decision signal builds up linearly from the baseline until it reaches the threshold for saccade initiation. The distribution of saccade reaction times is generated because the rate of rise for saccade decision signals is chosen randomly 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).

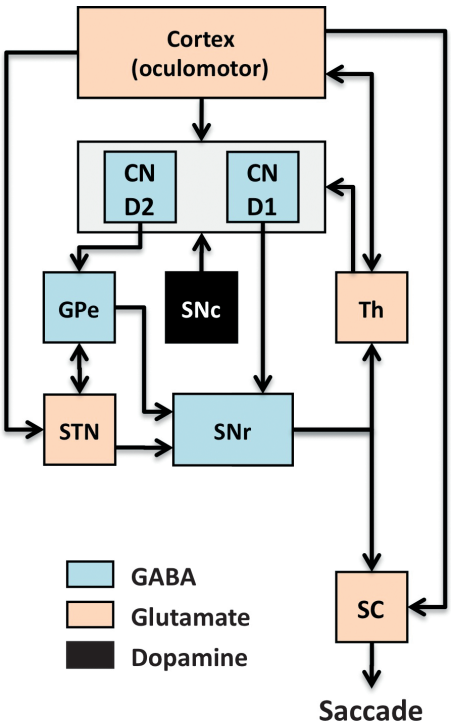

FIG. 3. Traditional BG model for saccade control. SNc, substantia nigra pars compacta; Th, thalamus. CN D1 indicates CN neurons expressing dopamine D1-like receptors projecting to the SNr (direct pathway). CN D2 indicates CN neurons expressing dopamine D2-like receptors projecting to the GPe (indirect pathway). Several important anatomical connections are omitted to retain simplicity.

1995; Reddi *et al.*, 2003; Nakahara *et al.*, 2006). 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 the rate of rise in the decision signal and/or the distance between the baseline and threshold (Fig. 2A). This model is useful to infer how artificial manipulation of BG neural activity influences the saccade initiation process. For instance, Fig. 2B and C shows reaction time distributions without and with microstimulation delivered to the caudate nucleus (CN), respectively, while monkeys performed the prosaccade paradigm (Watanabe & Munoz, 2010a; 2011). In this case, the model fits better to the two distributions of reaction times under the assumption that CN microstimulation changed the rate of rise in the decision signal, rather than the assumption that CN microstimulation changed the distance between the baseline and threshold (Fig. 2A).

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

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 skeletomotor 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; Peltsch *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 irrepressive 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; Peltsch *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; Peltsch *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 (Bejjani *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 (Limousin *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; Camicioli *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

delivered (Chan *et al.*, 2005). It is not yet known whether SNr microstimulation induces timing errors during the visual delay saccade paradigm in behaving monkeys because microstimulation was delivered only after fixation point disappearance in the previous studies (Basso & Liu, 2007; Liu & Basso, 2008).

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 paradigms. 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 (Matsumura *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 glubus 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 innervations 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; Blekher *et al.*, 2006; Peltsch *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.*, 2003). 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

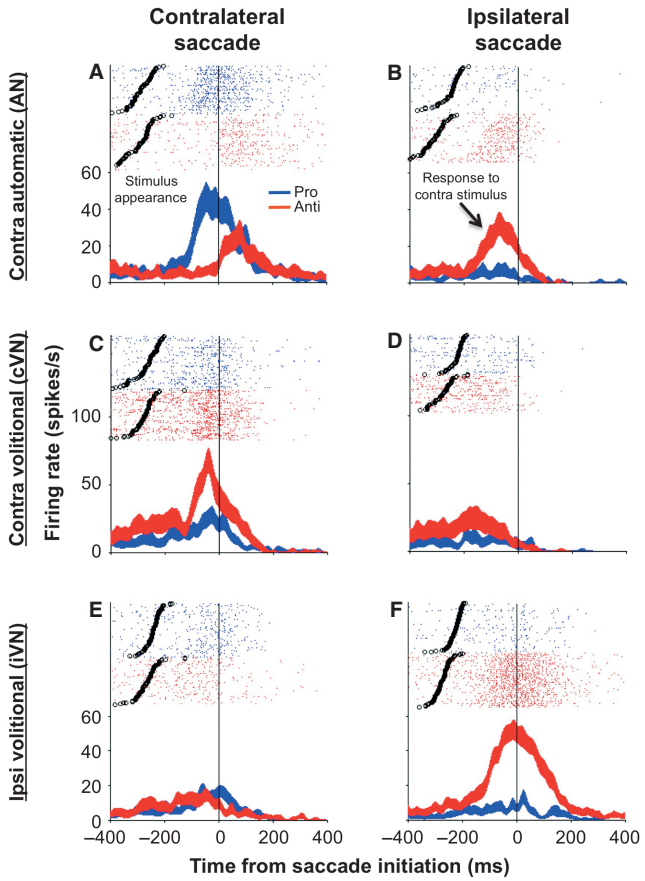

FIG. 4. Three types of caudate neurons during pro- and antisaccade paradigm. (A and B) Automatic neuron with contralateral saccade preference. This neuron responded to contralateral visual stimulus on ipsilateral antisaccade trials (red in B). (C and D) Volitional neuron with contralateral saccade preference. (E and F) Volitional neuron with ipsilateral saccade preference. Left (A, C and E) and right (B, D and F) columns indicate contralateral and ipsilateral saccade trials, respectively. Black circles indicate saccade initiation. Activity is aligned with saccade initiation. The same data have been shown previously (Watanabe & Munoz, 2010b).

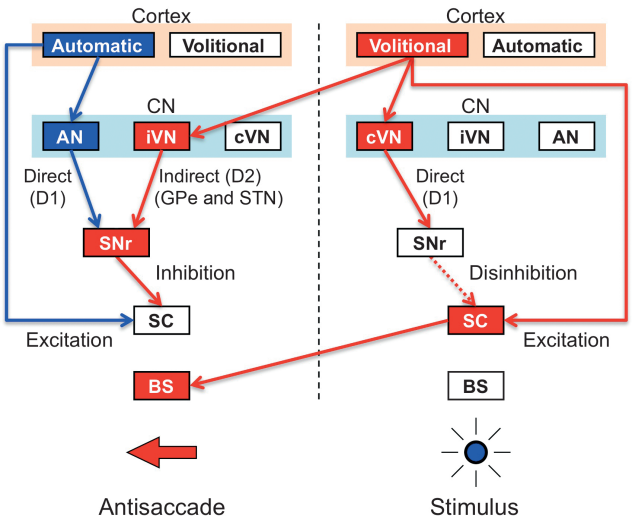

FIG. 5. Simple BG model for conflict resolution during the antisaccade paradigm. The appearance of a visual stimulus recruits a neural circuit facilitating an automatic direction error saccade toward the stimulus (blue). At the same time, another neural circuit is activated to generate a volitional antisaccade toward the opposite direction of the stimulus (red). In the BG, a group of CN neurons encoding contralateral automatic saccades [automatic neurons (ANs), Fig. 4A and B] give rise to the direct pathway (CN D1 in Fig. 3) and facilitate the direction error saccade. Another group of CN neurons encoding contralateral volitional saccades [contralateral volitional neurons (cVNs), Fig. 4C and D] give rise to the direct pathway (CN D1 in Fig. 3) and facilitate the correct antisaccade. The conflict between the automatic and volitional saccade commands is resolved by another group of CN neurons encoding ipsilateral volitional saccades [ipsilateral volitional neurons (iVNs), Fig. 4E and F], which give rise to the indirect pathway (CN D2 in Fig. 3) and attenuate the automatic saccade command by activating SNr neurons through the GPe and STN. BS, brainstem.

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 volitional 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; Scatton *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 express 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 (Liang *et al.*, 2008; see also Oye *et al.*, 1970; Calabresi *et al.*, 1993; Azdad *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; Perlmutter & 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 $GABA_A$ 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.

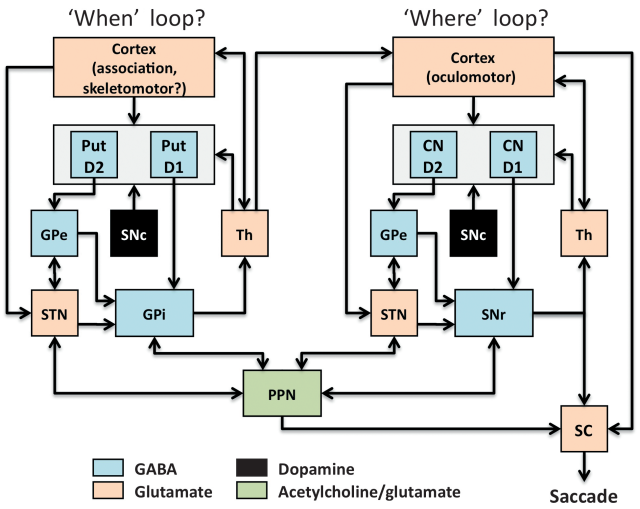

FIG. 6. Extended BG model for saccade control. The extended circuit (left – Put GPi) might determine when to initiate saccades, whereas the traditional circuit (right – CN-SNr) might determine where to direct saccades. Put, putamen. Put D1 indicates putaminal neurons expressing dopamine D1-like receptors projecting to the GPi (direct pathway). Put D2 indicates putaminal neurons expressing dopamine D2-like receptors projecting to the GPe (indirect pathway). Several important anatomical connections are omitted to retain simplicity. SNc, substantia nigra pars compacta; Th, thalamus.

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 because, 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; Ondo *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 (Russchen *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/brainstem 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-Motoshita *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 (Byne *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 (Russchen *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-Deseilligny *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 (Foote *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; Katsakiori *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

thalamic nuclei presumably influences both the cortex–BG and cortex–cerebellum 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 Brigell *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 saccade 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 GPi (Sadikot *et al.*, 1992a; Mouroux *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, GPi 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 subthalamotomy (STN lesion) is an effective surgical treatment for Parkinson's disease, whereas it could induce hemiballismus in normal BG (Guridi & Obeso, 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 saccade performance (e.g. reaction times, error rates). Such analyses could show whether saccade 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 GPi 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 GPi) 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 GPi do not have clear saccade direction preferences (Yoshida & Tanaka, 2009) and unilateral pallidotomy 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 PPN, 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. GPi 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 GPi DBS on passing fibers cannot be excluded. Controlled experiments in behaving monkeys, such as reversible inactivation of GPi 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; Grabli *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; PPN, pedunculopontine tegmental nucleus; SC, superior colliculus; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; Vim, ventral intermediate nucleus; VL, ventral lateral nuclei.

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