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Functional significance of the cortico–subthalamo–pallidal 'hyperdirect' pathway

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Abstract

How the motor-related cortical areas modulate the activity of the output nuclei of the basal ganglia is an important issue for understanding the mechanisms of motor control by the basal ganglia. The cortico–subthalamo–pallidal 'hyperdirect' pathway conveys powerful excitatory effects from the motor-related cortical areas to the globus pallidus, bypassing the striatum, with shorter conduction time than effects conveyed through the striatum. We emphasize the functional significance of the 'hyperdirect' pathway and propose a dynamic 'center-surround model' of basal ganglia function in the control of voluntary limb movements. When a voluntary movement is about to be initiated by cortical mechanisms, a corollary signal conveyed through the cortico–subthalamo–pallidal 'hyperdirect' pathway first inhibits large areas of the thalamus and cerebral cortex that are related to both the selected motor program and other competing programs. Then, another corollary signal through the cortico–striato–pallidal 'direct' pathway disinhibits their targets and releases only the selected motor program. Finally, the third corollary signal possibly through the cortico–striato–external pallido–subthalamo–internal pallidal 'indirect' pathway inhibits their targets extensively. Through this sequential information processing, only the selected motor program is initiated, executed and terminated at the selected timing, whereas other competing programs are canceled.

Keywords: Basal ganglia; Globus pallidus; Subthalamic nucleus; Hyperdirect pathway; Direct pathway; Indirect pathway; Motor control

1. Position of the subthalamic nucleus in the basal ganglia circuitry

The subthalamic nucleus (STN, corpus Luysi) is a relatively small nucleus of the basal ganglia and is located ventrally to the zona incerta and dorsally to the cerebral peduncle. In early 1980s, the STN has been considered to be part of a minor and closed ancillary loop in the basal ganglia circuitry that includes the external segment of the globus pallidus (GPe) (DeLong and Georgopoulos, 1981). In a more recent view, the striatum receives direct excitatory cortical inputs, and projects to the output nuclei i.e. the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNr) through two major projection systems, 'direct' and 'indirect' pathways (Albin et al., 1989; Alexander and Crutcher, 1990). The 'direct' pathway arises from GABAergic striatal neurons containing substance P, and projects monosynaptically to the GPi/SNr. The 'indirect' pathway arises from GABAergic striatal neurons containing enkephalin, and projects polysynaptically to the GPi/SNr by way of a sequence of connections involving the GPe and STN. Thus, the STN is considered to occupy a crucial position as a relay nucleus of the 'indirect' pathway. In addition, there has been growing evidence that the STN could be regarded as another input station of the basal ganglia besides the striatum (Mink and Thach, 1993; Kita, 1994; Mink, 1996; Levy et al., 1997; Nambu et al., 2000b), because the STN receives direct cortical projections, especially from the frontal lobe (Hartmann-von Monakow et al.,

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1978; Kitai and Deniau, 1981; Nambu et al., 1996, 1997). Moreover, the STN has recently been highlighted as a target structure of stereotaxic surgery for Parkinson's disease (Bergman et al., 1990).

In this article, we would like to characterize this new pathway of the basal ganglia circuitry through the STN, the cortico–STN–pallidal 'hyperdirect' pathway (see also Gerfen, 2000), and propose a dynamic 'center-surround model' of basal ganglia function in the control of voluntary limb movements.

2. STN as an input station of the basal ganglia

The STN receives direct cortical projections from wide areas of the frontal lobe (Hartmann-von Monakow et al., 1978). Such cortico–STN projections were considered to be sparse, and therefore have been regarded less important. However, recent anterograde double-labeling studies have shown that the monkey STN receives substantial somatotopically organized projections from the primary motor cortex (MI), the supplementary motor area (SMA), and the dorsal (PMd) and ventral (PMv) divisions of the premotor cortex (Nambu et al., 1996, 1997). The MI provides somatotopic projections predominantly to the lateral part of the STN ('MI domain'), whereas the SMA, PMd, and PMv provide those preferentially to its medial counterpart ('SMA/PM domain') (Fig. 1). Somatotopic representations in the lateral STN are arranged from medial to lateral in the order of the hindlimb, forelimb, and orofacial parts. In contrast, these body parts are represented inversely from lateral to medial in the medial STN, as if they are reflecting a mirror image against the somatotopic arrangement in the lateral STN. Through the cortico–STN projections, cortical stimulation evokes strong, short-latency excitatory responses in STN neurons (Kitai and Deniau, 1981; Ryan and Clark, 1992; Fujimoto and Kita, 1993; Kita, 1994; Maurice et al., 1998; Nambu et al., 2000b). Based on these anatomical and physiological observations, the STN is likely to function as another input station of the basal ganglia besides the striatum (Mink and Thach, 1993; Kita, 1994; Mink, 1996; Levy et al., 1997; Nambu et al., 2000b).

Discrete lesions in the STN result in violent involuntary movements involving the contralateral limbs, termed 'hemiballismus.' No correlation between the location of the STN lesion and the somatotopic specificity of dyskinesia has yet been revealed in hemiballismus (Whittier and Mettler, 1949; Carpenter et al., 1950; Carpenter and Carpenter, 1951; Hamada and

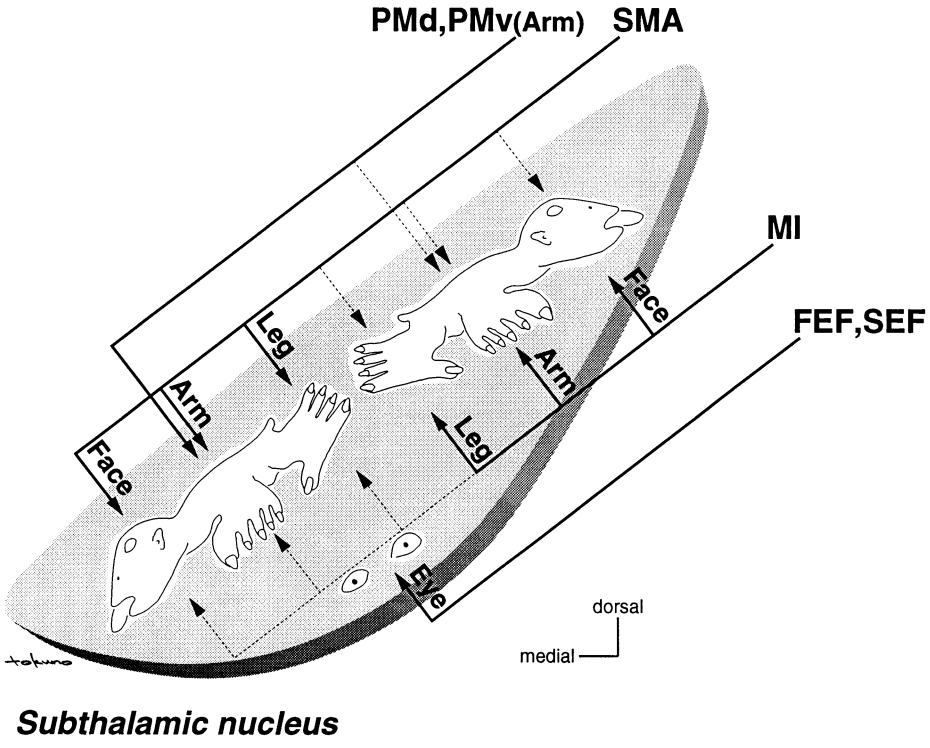

Fig. 1. Schematic diagram showing the organization of cortico–subthalamic (STN) inputs from the primary motor cortex (MI), the supplementary motor area (SMA), the dorsal (PMd) and ventral (PMv) divisions of the premotor cortex, the frontal eye field (FEF), and the supplementary eye field (SEF). Dotted lines indicate minor inputs. Note that inputs from the MI predominantly terminate in the lateral part of the STN ('MI domain') and those from the SMA, PMd and PMv in the medial part ('SMA/PM domain'). The somatotopy in each domain is reversed. (Modified from Nambu et al., 1996)

DeLong, 1992). The dyskinesia appeared more predominant and marked in the hindlimb than in the forelimb, and rare in the orofacial part. The reversed image of dual somatotopy in the STN may be able to account for the pathophysiology of hemiballismus by supposing that lesions spanning the homotopic zones of both the MI and SMA/PM domains are required for the development of dyskinesia (Nambu et al., 1996). When the mediolateral central part of the STN is affected, the hindlimb zones of both the MI and SMA/PM domains are subject to simultaneous lesions. On the other hand, so large lesions as to infringe on considerable parts of the STN are likely to destroy the forelimb and/or orofacial zones of both the MI and SMA/PM domains. In such a large-lesion case, the hindlimb zones of the MI and SMA/PM domains are constantly exposed to simultaneous lesions. The concurrent STN lesions in the homotopic zones of the MI and SMA/PM domains may affect a given body part more readily and severely.

3. Cortico–STN–pallidal 'hyperdirect' pathway

The STN receives inputs from the cerebral cortex and, in turn, sends outputs to the GPi/SNr. Cortical stimulation induces an early, short-latency excitation, followed by an inhibition and a late excitation in pallidal neurons of monkeys. The early excitation is considered to be derived from the cortico–STN–pallidal pathway based on the following findings (Nambu et al., 2000b). Simultaneous recordings of neuronal activity in the pallidal complex and STN have shown that the cortical stimulation induced an early, short-latency excitation in STN neurons preceding that in pallidal neurons. Stimulation in the STN through the recording electrode activated pallidal neurons orthodromically. Blockade of neuronal activity in the STN by injection of muscimol ($GABA_A$ receptor agonist) thereinto abolished the early and late excitations of pallidal neurons evoked by cortical stimulation. In addition, blockade of the glutamatergic cortico–STN neurotransmission by injection of (±)-3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid [CPP, *N*-methyl-D-aspartate (NMDA) receptor antagonist] into the STN suppressed the early excitation of pallidal neurons, whereas interference with the GABAergic pallido–STN neurotransmission by injection of bicuculline ($GABA_A$ receptor antagonist) into the STN had little effect on the early excitation. Similar results were also obtained from electrophysiological experiments in anesthetized rats, i.e. cortical stimulation evoked three phases of responses, consisting of an early excitation, an inhibition and a late excitation, in the globus pallidus (GPe of primates) and SNr (Ryan and Clark, 1991; Fujimoto and Kita, 1992; Kita, 1992, 1994; Maurice et al., 1999), and the early excitation disappeared after either permanent lesions of the STN (Ryan and Clark, 1991; Kita, 1992, 1994) or blockade of cortico–STN neurotransmission from the prefrontal cortex (Maurice et al., 1999).

The inhibition evoked in pallidal neurons by cortical stimulation is considered to be mediated by the cortico–striato–pallidal 'direct' pathway because (1) stimulation in the striatum evoked inhibitory responses in pallidal neurons and the difference between the latency of the inhibition evoked by cortical stimulation and that of the inhibition evoked by striatal stimulation corresponds well to the cortico–striatal conduction time (Yoshida et al., 1993), and (2) inhibitory postsynaptic potentials (IPSPs) or inhibition evoked by cortical stimulation was abolished by systemic injection of a GABAergic blocker (Kita, 1992) or by blocking cortico–striatal neurotransmission (Maurice et al., 1999). On the other hand, the origin of the late excitation evoked in pallidal neurons by cortical stimulation is ambiguous. It could be ascribed to the net excitatory cortico–striato–GPe–STN–GPi 'indirect' pathway because similar late excitatory responses of SNr neurons were markedly reduced after the blockade of the cortico–striatal or striato–GPe neurotransmission (Maurice et al., 1999). However, injection of CPP into the STN also attenuated the late excitation, suggesting the involvement of the cortico–STN–pallidal pathway in the late excitation of pallidal neurons (Nambu et al., 2000b). Moreover, a contribution of rebound firing after IPSPs via the 'direct' pathway cannot as yet be ruled out, because striatal stimulation caused rebound firing after IPSPs in pallidal neurons in slice preparations (Nambu and Llinás, 1994).

These observations indicate that the cortico–STN–pallidal pathway conveys powerful excitatory effects from the motor-related cortical areas to the pallidum, bypassing the striatum, with shorter conduction time than effects conveyed through the 'direct' and 'indirect' pathways (Fig. 2A). Based on these findings, we proposed to term this cortico–STN–pallidal pathway the 'hyperdirect' pathway of the basal ganglia (Nambu et al., 1996).

4. Functional significance of the cortico–STN–pallidal 'hyperdirect' pathway

Recent anatomical studies have shown that STN–pallidal fibers arborize more widely and terminate on more proximal neuronal elements than striato–pallidal fibers (Hazrati and Parent, 1992a,b). This suggests a 'center-surround model' of basal ganglia function which proposes focused selection and inhibition of competing motor programs (Mink and Thach, 1993; Mink, 1996; Hikosaka et al., 2000). Actually, analyzing the precise distribution of cortically evoked responses in the pallidum showed that neurons with typical excitation–

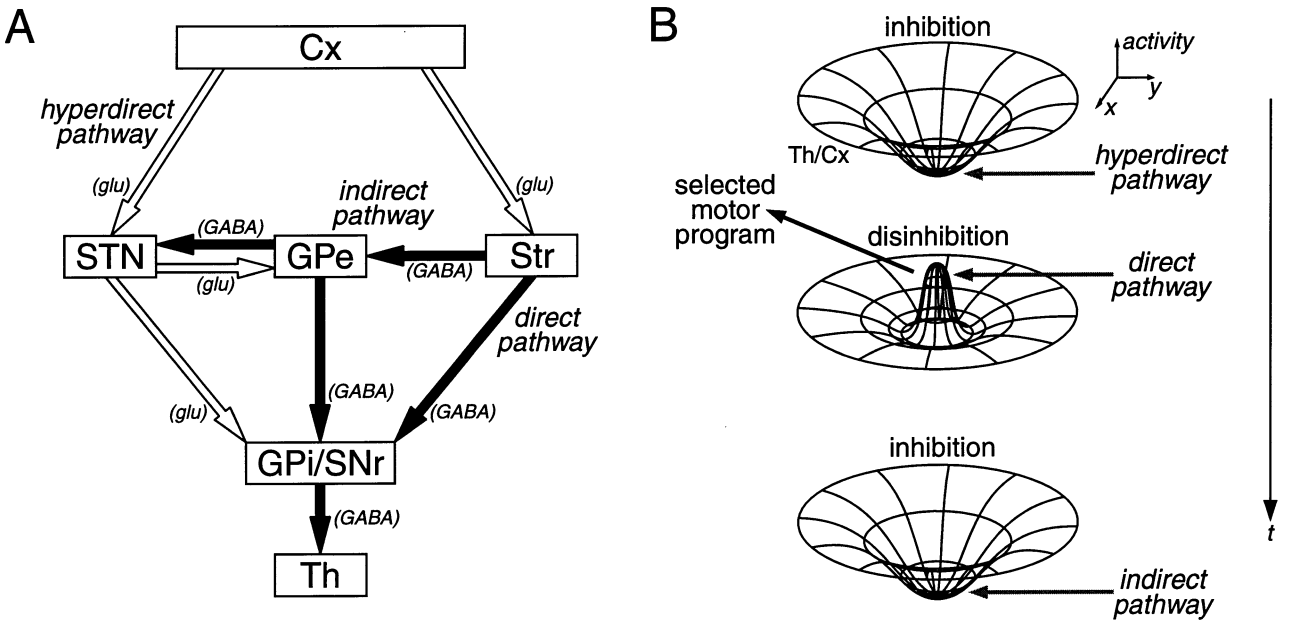

Fig. 2. (A) Schematic diagram of the cortico–STN–GPi/SNr 'hyperdirect' pathway, cortico–striato–GPi/SNr 'direct' pathway, and cortico–striato–GPe–STN–GPi/SNr 'indirect' pathway. Open and filled arrows represent excitatory glutamatergic (glu) and inhibitory GABAergic (GABA) projections, respectively. Cx, cerebral cortex; GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; Str, striatum; Th, thalamus. (B) Schematic diagram showing the dynamic aspects of the 'center-surround model' of basal ganglia function, which explains the activity changes in the thalamus and/or cortex (Th/Cx) caused by sequential inputs through the 'hyperdirect' (top), 'direct' (middle), and 'indirect' (bottom) pathways. (Modified from Nambu et al., 2000b)

inhibition–excitation responses had a tendency to be surrounded by neurons with only excitations, supporting the center-surround organization of the pallidum (unpublished observations).

The cortico–STN–pallidal 'hyperdirect' pathway exerts powerful excitatory effects on the output nuclei of the basal ganglia, and is faster in signal conduction from the cerebral cortex than the 'direct' and 'indirect' pathways (Fig. 2A). Based on these findings, we propose a dynamic model of basal ganglia function which expands the 'center-surround model' in the temporal domain in the regulation of voluntary limb movements (Fig. 2B; Nambu et al., 2000b). When a voluntary movement is about to be initiated by cortical mechanisms, a corollary signal is transmitted simultaneously from the motor cortex to the GPi through the cortico–STN–pallidal 'hyperdirect' pathway to activate GPi neurons extensively, thereby resulting in the inhibition of large areas of the thalamus and cortex that are related to both the selected motor program and other competing programs (Fig. 2B, top). Then, another corollary signal through the 'direct' pathway is conveyed to the GPi to inhibit a specific population of pallidal neurons in the center area. Such pallidal neurons disinhibit their targets and release only the selected motor program (Fig. 2B, middle). Finally, the third corollary signal possibly through the 'indirect' pathway reaches the GPi to activate neurons therein, suppressing their targets extensively (Fig. 2B, bottom). Through this sequential information processing, only the selected motor program is initiated, executed and terminated at the appropriate timing, whereas other competing programs mediated by pallidal neurons in the surrounding area are canceled. Actually, blockade of the STN neuronal activity (Hamada and Hasegawa, 1994; Nambu et al., 2000b) or lesions in the STN (Whittier and Mettler, 1949; Carpenter et al., 1950; Carpenter and Carpenter, 1951; Hamada and DeLong, 1992) resulted in induction of hemiballismus. These can be interpreted that motor programs usually inhibited by the STN are released at random timing. On the other hand, in the regulation of saccadic eye movements, Hikosaka et al. (2000) suggest the possibility that the 'indirect' pathway may also enhance the temporal contrast.

The difference of signals conveyed through the 'hyperdirect', 'direct' and 'indirect' pathways should be considered. Cortico–STN neurons and cortico–striatal neurons belong to distinct populations. The cortico–STN projections have been reported to originate from the axon collaterals of pyramidal tract neurons (Giuffrida et al., 1985), thus the STN receives and displays activity directly related to movements (Georgopoulos et al., 1983; DeLong et al., 1985; Wichmann et al., 1994). In contrast, cortico–striatal neurons transmit signals distinct from those sent to the spinal cord/brainstem, i.e. activity of cortico–striatal neurons is more selective to the parameters of behavioral tasks than that of cortico–peduncular neurons (Bauswein et al., 1989; Turner and

DeLong, 2000). Activity of striatal neurons resembles that of cortico–striatal neurons (Crutcher and DeLong, 1984; Crutcher and Alexander, 1990). Moreover, striatal neurons show context-dependent (Kimura, 1990; Kimura et al., 1992) or reward-contingent (Kawagoe et al., 1998) activity. Thus, the signals through the cortico–STN–pallidal 'hyperdirect' pathway may inhibit motor programs widely, and then the signals through the 'direct' pathway may adjust the selected motor program according to the situation.

5. Activity of pallidal and STN neurons during movements

The dynamic model of basal ganglia function presented in the previous section has been derived mainly from 'stimulation' studies. However, the cortico–STN–pallidal 'hyperdirect' pathway may actually contribute to the neuronal activity of the basal ganglia in a physiological state. Pallidal activity during voluntary limb movements always displays an increase rather than a decrease in discharge, and the incidence ratio of an increase to a decrease is 1.6–5.8 (Georgopoulos et al., 1983; Anderson and Horak, 1985; Mitchell et al., 1987; Hamada et al., 1990; Nambu et al., 1990; Mink and Thach, 1991; Turner and Anderson, 1997). In addition, the movement-related increase tends to occur earlier than the decrease in the GPi (Georgopoulos et al., 1983; Anderson and Horak, 1985). Neurons in the lateral STN (Georgopoulos et al., 1983; DeLong et al., 1985; Wichmann et al., 1994; Cheruel et al., 1996) and STN neurons projecting to the pallidal complex (Jinnai et al., 1990) also exhibit movement-related activity. The incidence ratio of an increase to a decrease of STN neurons is 2.4–9.0. Comparing the timing of movement-related pallidal and STN activity showed the earlier onset of activity in the STN than that in the pallidum (Georgopoulos et al., 1983; Cheruel et al., 1996). Based on these observations, activity of STN neurons during voluntary limb movements is likely to be mediated by the excitatory cortico–STN projection rather than by the inhibitory GPe–STN projection. Such increased STN activity may contribute to increased activity of pallidal neurons. Thus, it is most likely that the increased pallidal activity during voluntary limb movements is mediated by the net excitatory, faster cortico–STN–pallidal 'hyperdirect' pathway, while the decreased pallidal activity is mediated by the net inhibitory, slower 'direct' pathway. The former is more frequent than the latter, and this could be explained by hypothesizing that the pallidal neurons with increased activity may represent those in the surrounding area of the selected motor program, and the pallidal neurons with decreased activity may represent those in the center area, whose number should be much smaller than that in the surrounding area. This situation also fits well with the proposed, dynamic 'center-surround model' (Fig. 2B).

On the other hand, SNr neurons show a reduction in discharge during saccadic eye movements and the reduced SNr activity is believed to disinhibit superior collicular neurons and finally evoke saccadic eye movements ('disinhibition model'; Hikosaka and Wurtz, 1983a,b). In addition, neurons in the ventral STN increase activity during eye fixation and decrease activity during saccadic eye movements (Matsumura et al., 1992). Such STN activity may enhance a change of SNr activity during saccadic eye movements through the excitatory STN–SNr projections. The applicability of the cortico–STN–pallidal 'hyperdirect' pathway to saccadic eye movements should be studied in the future.

The timing of movement-related pallidal and STN activity has been reported to be late compared to the activation of agonist muscles (Georgopoulos et al., 1983; Anderson and Horak, 1985; Mitchell et al., 1987; Mink and Thach, 1991; Wichmann et al., 1994; Turner and Anderson, 1997), suggesting that the output of the basal ganglia is unlikely to initiate movements (Mink, 1996). On the other hand, some studies reported that activity changes of pallidal and STN neurons were early enough to initiate movements (Nambu et al., 1990; Cheruel et al., 1994, 1996). The contribution of the basal ganglia output to the motor cortical activity should further be studied.

6. Unsolved problems

In this article, we have emphasized the functional significance of the cortico–STN–pallidal 'hyperdirect' pathway and the dynamic 'center-surround model' of basal ganglia function. In the next stage, it should be attested whether this model in relation to the 'hyperdirect' pathway actually functions in a physiological state by observing the effect of blocking cortico–STN neurotransmission on pallidal activity during the execution of behavioral tasks.

The contribution of the net inhibitory GPe–STN–GPi and/or inhibitory GPe–GPi pathways to GPi activity should also be tested. GPi activity should strongly be modulated by GPe activity if these inhibitory pathways actually work. However, neuronal activity in the GPe and GPi that has so far been observed in response to cortical stimulation and during the performance of motor tasks is very similar to each other (Georgopoulos et al., 1983; Anderson and Horak, 1985; Mitchell et al., 1987; Hamada et al., 1990; Nambu et al., 1990; Mink and Thach, 1991; Yoshida et al., 1993; Turner and Anderson, 1997; Nambu et al., 2000b). These neurons behave as if they are exclusively under the control of the cortico–STN–pallidal 'hyperdirect'

and cortico–striato–pallidal 'direct' pathways. Parent and Hazrati (1995) raised a question as to the existence of the 'indirect' pathway. To answer these problems, it is critical to characterize more explicitly the effects of the 'hyperdirect', 'direct' and 'indirect' pathways on the activity of pallidal neurons during the execution of behavioral tasks.

The model presented in this article may still be oversimplified and disregard some neuronal connections. The centromedian–parafascicular complex (CM–Pf) of the thalamus, which receives inputs from the GPi and cortex, projects massively to the striatum and less massively to the STN (Sadikot et al., 1992), emphasizing another similarity of the striatum and STN as input stations. Although the functional significance of these projections is not well analyzed, they may supply the input stations (i.e. the striatum and STN) with outputs of the basal ganglia, and may work as feedback loops. Recently, Matsumoto et al. (2001) have shown that neurons in the CM–Pf supply striatal neurons with information about behaviorally significant sensory events that can activate conditional responses of striatal neurons.

Finally, we would like to point out the validity of the dynamic 'center-surround model' proposed in this article for understanding the pathophysiology of basal ganglia disorders. The mechanisms underlying hypokinetic or hyperkinetic disorders are currently explained as the changes in the static state of the basal ganglia i.e. an increase or a decrease in the mean firing rate of GPi/SNr neurons which is likely to be caused by the imbalance between the 'direct' and 'indirect' pathways (DeLong, 1990). However, based on the dynamic 'center-surround model' as shown in Fig. 2B, the akinesia observed in the Parkinson's disease could better be explained by the reduction of the disinhibition in the thalamus and cortex through the 'direct' pathway in the spatial and temporal domains (Boraud et al., 2000; Nambu et al., 2000a). The dynamic model of basal ganglia function may lead us to better understanding of the pathophysiology of basal ganglia disorders, as well as of the normal functions of the basal ganglia.

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