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Review

Cause of parkinsonian symptoms: Firing rate, firing pattern or dynamic activity changes?

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ABSTRACT

Malfunctions of the basal ganglia cause movement disorders, such as Parkinson's disease and dystonia. Several models have been proposed to explain the pathophysiology of these disorders: (1) firing rate model: activity imbalance between the *direct* and *indirect* pathways changes the mean firing rates of the output nuclei of the basal ganglia and induces hypokinetic or hyperkinetic movement disorders; (2) firing pattern model: oscillatory and/or synchronized activity observed in the diseased basal ganglia disturbs information processing in the basal ganglia, resulting in motor symptoms; (3) dynamic activity model: abnormal neuronal modulations through the *hyperdirect*, *direct* and *indirect* pathways interfere with the sequential, dynamic activity changes, and disrupt the balance between the movement-related inhibition and its surrounding excitation in the output nuclei, leading to motor symptoms. In this mini-review, we will critically discuss the three models.

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Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the progressive loss of nigrostriatal dopaminergic (DAergic) neurons originating from the substantia nigra pars

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compacta (SNc). The loss of DAergic neurons induces severe motor and non-motor dysfunctions, such as akinesia, tremor, rigidity, postural instability, cognitive impairments and depression. There have been two major hypotheses that explain the pathophysiology of PD. First, the "firing rate model" was originally proposed based on firing rate changes of the basal ganglia (BG) neurons in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD monkeys [1]. These changes are considered to finally increase mean firing rates in the output nuclei of the BG, i.e., the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNr), along the BG pathways, and induce motor dysfunctions. However, some recent electrophysiological studies using MPTP-induced PD monkeys have failed to detect expected firing rate changes in the BG neurons [2–4]. Second, unit activity and local field potentials (LFPs) recorded from PD animals and patients have shown oscillatory and synchronized activity in the BG [3,5–8]. These firing pattern changes may cause the disturbance of information processing in the BG, resulting in motor dysfunctions [5]. This "firing pattern model" seems to have now largely supplanted the "firing rate model". In this mini-review, we would like to compare and critically discuss these two models. In addition, we would like to introduce a novel "dynamic activity model" [9] that seems to better explain the pathophysiology of PD and may eventually replace the preceding two models.

Firing rate model

One of the earliest studies using MPTP-treated PD monkeys demonstrated a reduction of activity in the external segment of the globus pallidus (GPe) and increased activity in the subthalamic nucleus (STN) and GPi [1]. Together with the *direct* and *indirect* pathways model of the BG [10–13], the pathophysiology of PD is explained as follows (Fig. 1A). Dopamine (DA) depletion reduces tonic excitation to striatal *direct* pathway neurons projecting to the GPi and tonic inhibition to striatal *indirect* pathway neurons projecting to the GPe [10,12–14]. Both of these changes are thought to increase mean firing rates of GPi/SNr neurons through the inhibitory striato-GPi/SNr *direct* pathway and the net excitatory striato-GPe-STN-GPi/SNr *indirect* pathway. Such increased activity in the BG output nuclei seems to induce decreased activity in thalamic and cortical neurons, resulting in akinesia. A number of studies subsequent to the original one confirmed similar activity changes: reduced firing rates in the GPe and increased firing rates in the STN and GPi in the PD state [15–21]. A recent optogenetic study has elegantly shown that facilitating striatal *direct* pathway neurons in PD mice ameliorates akinesia, and that facilitating striatal *indirect* pathway neurons in normal mice induces akinesia [22].

The "firing rate model" seems to be applicable to hyperkinetic disorders that exhibit involuntary movements, as well. Neuronal activity recording in hyperkinetic disorders revealed reduced activity in the GPi. The development of the involuntary movements can be explained as the result of reductions in inhibitory BG outputs to the thalamus. In dystonia, a number of single cell recording studies in patients undergoing functional neurosurgery have reported that firing rates in the GPe and GPi are low [23–26], although some study reported that firing rates were found to be as high as in PD patients [27]. An animal model of dystonia also reported decreased firing rates and the appearance of burst firings in the GPe and GPi [28]. In addition, in experimental models of hemiballism induced by electrolytic lesion, chemical lesion or chemical inactivation of the STN [29–31], ballistic movements were accompanied by substantial reduction of firing rates in the GPe and GPi. It is a consequence of reduced glutamatergic inputs from the STN to the GPe and GPi. The injection of a GABA-receptor blocker into the GPe also induced dyskinetic movements [32–34], probably through STN inhibition by enhanced inhibitory GPe-STN transmission.

Mechanism of firing rate changes

The "firing rate model" assumes that DA has excitatory effects on striato-GPi *direct* pathway neurons through DA D1 receptors (D1Rs) and inhibitory effects on striato-GPe *indirect* pathway neurons through D2 receptors (D2Rs) (Fig. 1A). DA effects were originally proposed on the basis of indirect measurement of neuronal activity, such as alterations in gene expression, glucose utilization and receptor binding [13,35], and have also been confirmed electrophysiologically [35–38]. In addition, DA regulates corticostriatal synaptic plasticity: D1R signaling induces

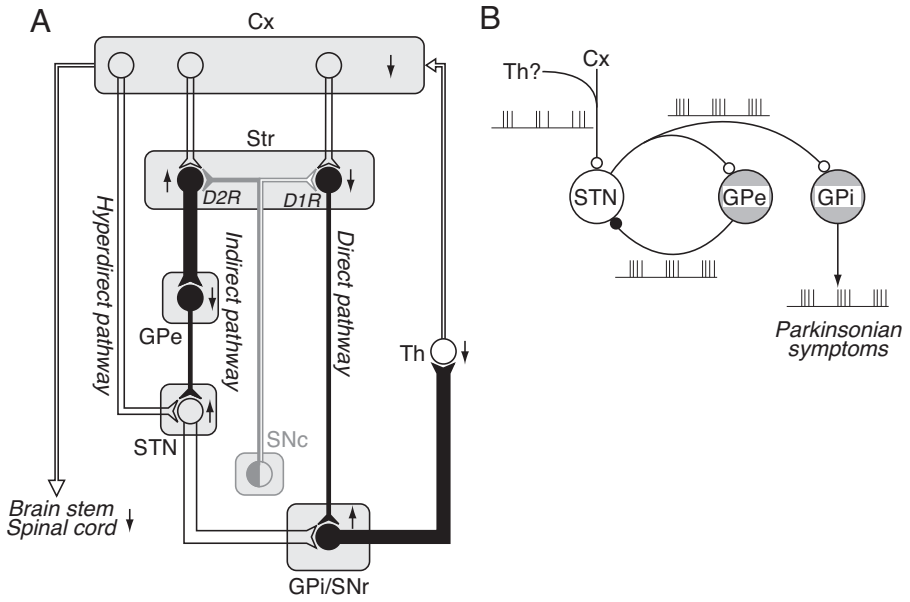

Fig. 1. "Firing rate" (A) and "firing pattern" (B) models explaining the pathophysiology of Parkinson's disease. Open and filled symbols represent excitatory and inhibitory neurons, respectively. Cx, cerebral cortex; D1R, D2R, dopamine D1 and D2 receptors; GPe and GPi, external and internal segments of the globus pallidus; SNc and SNr, substantia nigra pars compacta and reticulata; STN, subthalamic nucleus; Str, striatum; Th, thalamus.
(A) Modified from DeLong [12]; (B) modified from Tachibana et al. [46].

long-term potentiation, while D2R signaling induces long-term depression [35,36,39]. DA depletion changes the density and morphology of dendritic spines on striatal projection neurons [40], and may modify corticostriatal transmission. DAergic projections to other BG structures may also contribute to the excitability changes [41,42].

Criticism of the firing rate model

The "firing rate model" met with the following criticisms. (1) Recent other studies have reported no changes in GPe or GPi firing rates, or rate changes opposite to those predicted by the model [2–4,43–46]. (2) Inactivation of the GPi in normal monkeys does not induce severe motor deficits nor involuntary movements as predicted by the model [47,48]. Instead, pallidotomy in PD patients abolishes L-DOPA-induced dyskinesia [49]. It should be noted, however, that in hyperkinetic disorders, firing rates of GPi neurons are indeed decreased as mentioned above. (3) Lesions in the thalamus do not produce akinesia [50]. Instead, thalamotomy in PD ameliorates PD symptoms [51]. Lesions in the GPe do not produce PD symptoms [21], while activation of the GPe induces dyskinesia [32–34]. (4) The firing rate changes cannot explain the mechanism of tremor and rigidity. (5) GPi activity seems to be increased through the striato-GPi and striato-GPe-STN-GPi pathways. However, sequential activity changes along the pathways leading to increased GPi activity have not been directly demonstrated.

Firing pattern model

The "firing pattern model" suggests that oscillatory and/or synchronized firings of the BG may disable individual neurons to process and relay motor-related information, resulting in the failure of appropriate movements [5] (Fig. 1B). Abnormal firing patterns, such as bursts and oscillations, were recorded in the BG of PD animals and patients. Oscillatory LFPs, which are supposed to be linked to oscillatory and synchronized firings of a large population of neurons [52], were also recorded from the BG of PD patients using electrodes for deep brain stimulation (DBS).

Burst activity

"Burst" means a series of firings at short periods of time. In the normal state, GPi, GPe and STN neurons fire randomly and usually do not fire in bursts: GPi neurons fire continuously at high frequency, GPe neurons fire at high frequency with pauses, and STN neurons fire continuously at a middle frequency range. Bursting neurons are increased in MPTP-treated PD monkeys and human PD patients [1,2,16,21,43,53–55].

Oscillatory activity in the tremor frequency and beta frequency bands

If burst activity occurs periodically, it becomes oscillatory activity. Oscillatory firings have been reported in the GPe, GPi and STN of PD animals and patients [3,6,16,19,43,46,56]. The range is in the tremor frequency (4–9 Hz) and beta frequency (10–30 Hz) bands. STN inactivation [57] or DA replacement therapy [46,56] ameliorates PD symptoms and oscillatory firings. Simultaneously recorded neurons in the GPe and GPi of PD monkeys exhibited synchronized oscillation [3,19,56,58], while neighboring pairs of neurons in the GPe/GPi under normal conditions did not exhibit correlation. Furthermore, the oscillatory firings are in synchrony between the STN, GPi and cortex [59,60]. Oscillatory LFPs, especially those in the beta frequency band, are also frequently observed using DBS electrodes in PD patients [7,8,61–64]. The amelioration of akinesia and rigidity by treatments with drugs or stereotactic surgery is correlated with the suppression of the oscillatory LFPs in the beta frequency band, and thus it is thought to be anti-kinetic [61].

Oscillatory activity in the gamma frequency band

In addition to the low frequency activity, oscillatory LFPs in the high, gamma frequency (>60 Hz) band are also observed. In contrast to the low frequency band activity being anti-kinetic, the gamma frequency band activity is believed to be pro-kinetic, because oscillatory LFPs in the gamma frequency band were increased in response to DA replacement therapy and decreased in the PD state [61,62].

Mechanism of oscillatory activity

It is probable that BG oscillations are generated by local circuits within the BG. The most probable candidate of such oscillators is the GPe-STN complex (Fig. 1B). Oscillations are produced by the GPe-STN inhibitory and STN-GPe excitatory connections [46,65–67]. DA may have a role in de-correlating neuronal activity, and DA depletion may enhance connections between the GPe and STN, and promote oscillatory activity [68–70]. Rhythmic cortical inputs to the STN also contribute to oscillatory activity in the STN-GPe-GPi network [46]. Hyperactivity of the cortico-STN *hyperdirect* or striato-GPe *indirect* pathway may underlie a tendency for oscillatory activity [69–71]. Plastic changes inside and outside the striatum may also enhance oscillatory activity [40,42].

Criticism of the firing pattern model

The explanation for akinesia by the "firing pattern model" is not as straightforward as that by the "firing rate model". Besides, the "firing pattern model" met with the following criticisms. (1) The causal relationship between the emergence of BG oscillation and the PD symptoms is questionable. During chronic DA depletion induced by MPTP in monkeys, oscillatory activity did not precede, but followed the appearance of PD motor symptoms [44], denying a causal relationship. (2) Acute disruption of DA transmission induced catalepsy, but did not develop oscillatory activity, which is distinct from chronically DA depleted animals [72]. (3) The exact origin of LFPs in the GPi and STN is unclear. In the cortex, synchronous excitatory postsynaptic potentials in pyramidal neurons produce open-field potentials, which can be readily recorded as LFPs [73]. On the other hand, neurons in the deep nuclei, such as GPi and STN, produce closed-field potentials, which are not detectable outside their dendritic fields. Thus, the origin of LFPs in the GPi and STN and their relation to neuronal firings should be carefully investigated.

Dynamic activity model

We would like to propose a novel "dynamic activity model", which can better explain the pathophysiology of PD (Fig. 2) [9,74,75]. According to this model, in the normal state, signals through the cortico-STN-GPi/SNr *hyperdirect*, cortico-striato-GPi/SNr *direct* and cortico-striato-GPe-STN-GPi/SNr *indirect* pathways cause dynamic activity changes in the GPi/SNr and release only a selected motor program at a selected timing with a clear boundary between the selected and other unnecessary competing motor programs (Fig. 2A). GPi/SNr neurons receive competitive, sequential inputs from the *hyperdirect*, *direct* and *indirect* pathways that originate from the cortex. Signals through the *direct* pathway disinhibit thalamic neurons in the *center* area, which are related to a selected motor program, while those from the preceding *hyperdirect* and succeeding *indirect* pathways inhibit them to make clear initiation and termination of the selected motor

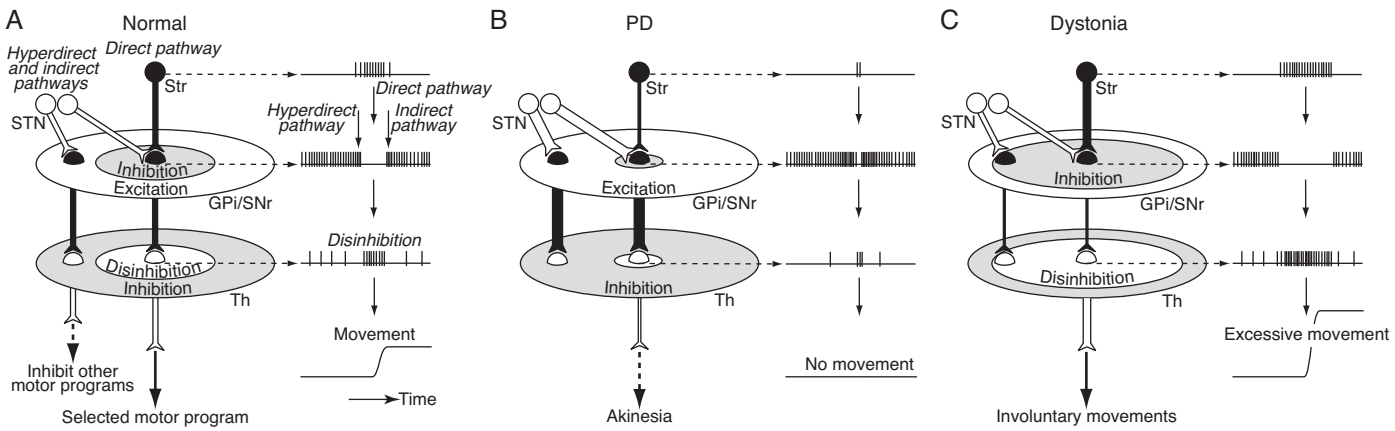

Fig. 2. "Dynamic activity model" explaining the control of voluntary movements in the normal state (A), and the pathophysiology of Parkinson's disease (PD) (B) and dystonia (C). Spatial distributions (*left* in each panel) and temporal patterns (*right* in each panel) of neuronal activity in the striatum (Str), GPi/SNr and thalamus (Th) during movements are illustrated.
Modified from Nambu [9].

program (Fig. 2A, right). On the other hand, in the *surrounding* area, signals through the *hyperdirect* and *indirect* pathways continuously inhibit thalamic neurons, which are involved in other unnecessary competing motor programs, with a minimal contribution from the *direct* pathway (Fig. 2A, left). Sequential inputs to the GPi/SNr from the cortex through the *hyperdirect*, *direct* and *indirect* pathways have been vigorously confirmed by cortically evoked excitation-inhibition-excitation responses in the GPi/SNr of rodents, primates and human patients [28,31,76–79]. In addition, the *center-surround* composition shown in Fig. 2A is based on the anatomical study showing that excitatory STN–GPi fibers arborize more widely and terminate on more proximal neuronal elements than inhibitory striato–GPi fibers [80].

In the PD state, DA depletion reduces movement-related GPi inhibition through the *direct* pathway in the *center* area and facilitates movement-related GPi excitation through the *hyperdirect* and *indirect* pathways in the *center* and *surrounding* areas (Fig. 2B). These changes shorten (Fig. 2B, right) and narrow (Fig. 2B, left) movement-related GPi inhibition, which leads to the reduction of disinhibition in the thalamus and cortex, resulting in akinesia. In fact, the ratio of the number of activated to that of inhibited GPi neurons during movements was increased after MPTP-treatment [81,82]. Increased activity through the *hyperdirect* and *indirect* pathways and decreased activity through the *direct* pathway were suggested by testing cortically evoked responses in the GPi/SNr of PD rodents [83–85]. In addition, the "dynamic activity model" can simultaneously explain the pathophysiology of hyperkinetic disorders as well. Enhanced movement-related inhibition in the *center* area of the GPi through the *direct* pathway, which is longer and wider, and reduced GPi excitation through the *hyperdirect* and *indirect* pathways in the *center* and *surrounding* areas result in excessive, uncontrolled disinhibition in the thalamus and cortex (Fig. 2C), leading to involuntary movements [28,31,78,86].

Firing rate and firing pattern changes in the dynamic activity model

Alterations of dynamic activity in the GPi may be a fundamental feature of PD, and firing rate and firing pattern changes may be merely epiphenomena. Activity changes through the *hyperdirect*, *direct* and *indirect* pathways exclusively modulate movement-related phasic activity and may not be strong enough to modulate spontaneous firing rates. Thus, it seems to be natural that no apparent changes are observed in the mean firing rates. In addition, under normal conditions, the activity balance between the *hyperdirect*, *direct* and *indirect* pathways contributes to appropriate, timely activation of BG neurons and does not induce oscillation. On the other hand, under PD conditions where the activity balance between the three pathways collapses, spontaneous cortical activity can easily induce oscillatory activity in the BG [69–71], which is detected as firing pattern changes.

Points to be solved in the dynamic activity model

The "dynamic activity model" may have the following points to be solved. (1) It is still paradoxical that GPi inactivation does not induce dyskinesia in the normal state, but that instead, GPi lesioning is used for the treatment of dyskinesia in PD. However, this can be explained by the assumption that a certain level of remaining GPi activity is necessary to induce involuntary movements. In L-DOPA-induced dyskinesia in PD, signals through the *hyperdirect*, *direct* and *indirect* pathways may induce a sequence of bursts and pauses in the GPi, and subsequent inhibition and rebound bursts in the thalamus and cortex, leading to the manifestation of involuntary movements. (2) Lesions in the thalamus do not produce akinesia in the normal state. This can be explained by that cerebellar inputs to the thalamus may compensate for the initiation of movements. (3) Activity changes in the BG induced by the *hyperdirect*, *direct* and *indirect* pathways begin at the timing of movement onset, and thus, may be too late for movement initiation in the normal state. This point should be examined carefully whether dynamic activity changes in the BG can contribute to the manifestation of abnormal movements in BG disorders. (4) The *center-surround* composition in the "dynamic activity model" is hypothetical and is not yet proven. Although an anatomical study does support this configuration [80], other studies rather suggest highly specific STN–GPi and striato-GPi projections [87,88]. Further investigation is needed to determine the topographical distribution of striatum-derived inhibition and STN-derived excitation in the GPi upon cortical stimulation. (5) It is still unknown how cortical activation during voluntary movements contributes to the activity changes in the GPi. It has been confirmed that electrical cortical stimulation does induce a series of responses composed of excitation-inhibition-excitation in the GPi through the *hyperdirect*, *direct* and *indirect* pathways [31,77]. As a next step, recording GPi activity from behaving animals is essential to solve this question. Investigation of movement-related GPi activity under conditions of PD and hyperkinetic disorders will also help toward verifying the "dynamic activity model". (6) In addition to the ascending projections to the thalamus, output from the BG descends to the

brain stem and control various types of behaviors, such as rhythmic limb movements and postural muscle tone [89]. The contribution of the BG-brain stem pathway to symptoms of movement disorders remains to be studied.

Conclusions

In this mini-review, we have critically evaluated three models to explain pathophysiology of movement disorders, especially PD: the "firing rate", "firing pattern" and "dynamic activity" models. Among them, the "dynamic activity model" seems to better explain the symptoms of movement disorders and provide unified mechanisms for hypokinetic and hyperkinetic disorders. Further studies including the recording of movement-related BG activity in animal models of PD and hyperkinetic disorders will be necessary to verify the "dynamic activity model".

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