Update on models of basal ganglia function and dysfunction

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SUMMARY

Circuit models of basal ganglia function and dysfunction have undergone significant changes over time. The previous view that the basal ganglia are centers in which massive convergence of cortical information occurred has now been replaced by a view in which these structures process information in a highly specific manner, participating in anatomical and functional modules that also involve cortex and thalamus. In addition, much has been learned about the intrinsic connections of the basal ganglia. While the basal ganglia-thalamocortical circuitry was originally seen almost exclusively in its relationship to the control of movement, these structures are now viewed as essential for higher level behavioral control, for instance in the regulation of habit learning or action selection. Probably the greatest benefit of these models has been that they have motivated a wealth of studies of the pathophysiology of movement disorders of basal ganglia origin, such as Parkinson's disease. Such studies, in turn, have helped to reshape the existing circuit models. In this paper we review these fascinating changes of our appreciation of the basal ganglia circuitry, and comment on the current state of our knowledge in this field.

1. Anatomic models of the basal ganglia-thalamocortical circuitry

Because the basal ganglia were believed to receive input from large areas of the frontal cortex, to process and integrate information, and to send output to the motor cortex via the thalamus, early models emphasized a 'funneling' and 'selection' function of the basal ganglia [1]. It was proposed, that the basal ganglia selected the appropriate input based on the current context and sent the appropriate command to the motor cortex. Cerebellar and basal ganglia outputs were believed to converge at the thalamic level. This model has since been replaced by the 'segregated circuit' model, in which the basal ganglia are seen as components of a family of parallel, re-entrant loops, over which information, sent from individual cortical areas is processed in specific and mostly non-overlapping territories of the basal ganglia, and then returned to the respective frontal lobe area of origin via the thalamus.

A precursor of this modular model was described in 1981 by DeLong and Georgopoulos [2], based on physiologic and anatomic observations in primates which revealed segregated motor and non-motor areas in the basal ganglia and basal ganglia. This model was further expanded in the mid 1980s with the description of five functionally distinct 'circuits', i.e., a 'motor,' 'oculomotor', a 'dorsolateral prefrontal', a 'lateral orbitofrontal' and an 'anterior

cingulate' (limbic) circuit [3]. In this model, the motor circuit is centered on the supplementary motor area, with inputs from the motor cortex and the premotor areas. These cortical motor areas project topographically to the post-commissural putamen which sends efferents to the ventrolateral internal pallidal segment (GPi) and the caudolateral substantia nigra pars recticulata (SNr). The motor areas of GPi/SNr project, in turn, to portions of the ventral anterior and ventrolateral thalamus (VA/VL), which then return output to the SMA, with lesser projections to premotor and motor cortices. Neuronal specificity and somatotopy are maintained throughout the circuit. In a similar fashion, separate cortical and subcortical basal ganglia and thalamic areas are involved in the other basal ganglia circuits. A further extension has come from viral retrograde tracing studies (reviewed in [4]) which have shown that each of the larger cortico-subcortical circuits is comprised of multiple segregated subcircuits, centered on individual cortical areas.

While the segregated circuit hypothesis emphasizes segregation, some degree of convergence cannot be ruled out. For instance, it has been demonstrated that the basal ganglia-thalamocortical loops are not always closed [5]. In fact, studies using trans-synaptic transport of rabies virus to trace anatomical connections have indicated that regions of the basal ganglia that receive 'limbic' input project to the motor cortex (e.g., [6]). Inter-loop spread of information has also been proposed to occur at the level of the dopaminergic substantia nigra pars compacta (SNc) which may participate in spiral-like interactions with the striatum by which striatal inputs into the limbic SNc area may be projected into other areas of the

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striatum [7]. To date, however, there is no clear physiologic evidence for the spiral hypothesis.

Finally, while the original model emphasized the separation of basal ganglia and cerebellar cortical-subcortical circuits, recent evidence indicates that cerebellar output reaches the striatum via the thalamus [8], and that basal ganglia output from the STN reaches the cerebellum [9]. There is also evidence that cerebellar and basal ganglia outputs converge on the same cortical areas (e.g., [10–12]). These findings raise new questions regarding the functional segregation between basal ganglia and cerebellar circuits.

It should be noted, that, although the aforementioned models are centered on the interactions between the basal ganglia and cortex, the basal ganglia also project to the brainstem, in particular the pedunculopontine nucleus (PPN) and to the superior colliculus (SC). The GPi–PPN projection may play a significant role in locomotion and the SNr–SC projection in the control of eye and head movements. GPi projections also are directed to the lateral habenula and appear to play a role in reward mechanisms.

2. Connections between basal ganglia nuclei

Modern anatomical models of the intrinsic circuitry of the basal ganglia were developed in the 1980s [13–16]. In these models, the striatum is linked to GPi and SNr via a monosynaptic 'direct' striatal projection, and an 'indirect pathway', which includes projections to GPe, and from GPe to GPi, both directly and via the intercalated STN. With the exception of the glutamatergic STN projections, all of the intrinsic and output projections of the basal ganglia are GABAergic and inhibitory. Direct and indirect pathways originate from different populations of striatal projection neurons, whose activity is strongly dependent on their cortical inputs. The activity at corticostriatal synapses (and thus, the activity of direct and indirect pathways) is regulated by striatal dopamine, supplied via the massive nigrostriatal projection from the SNc.

In the classic formulation of the model, the different polarities of the direct and indirect pathways were thought to lead to different effects at the level of the basal ganglia output nuclei. Activation of direct pathway neurons would lead to inhibition, while activation of neurons of the indirect pathway would lead to disinhibition of GPi/SNr neurons. Because basal ganglia output is inhibitory, reduction of basal ganglia output through activation of the direct pathway would disinhibit thalamocortical activity, while activation of the indirect pathway would increase the inhibition of thalamocortical projections.

The direct and indirect pathways also differ in other aspects. Direct pathway neurons express substance P, while indirect pathway neurons contain enkephalin. In addition, direct pathway neurons express D1-family dopamine receptors, while indirect pathway neurons express D2-family receptors [17]. Studies in rodents have also suggested that the direct and indirect pathways receive inputs from distinct groups of cortical neurons [18], but these results are difficult to reconcile with primate studies in which cortical neurons, activated by antidromic stimulation of the putamen, were identified as slowly-responding non-pyramidal cells of low activity [19,20]. Finally, anatomic studies have shown that the separation of direct and indirect pathways is less than initially thought, due to extensive collaterals [21].

While most of the proposed movement-related functions of the basal ganglia-thalamocortical circuits, such as roles in the sequencing of movements, in the generation of internally generated or habitual movements are not well explained in a mechanistic sense, attempts have been made to explain two movement-related functions, 'scaling' and 'focusing', on the basis of the direct/indirect pathway organization of the basal ganglia. It was hypothesized that the basal ganglia serve roles in controlling the speed and amplitude of movement, by allowing movements to occur via activation of the direct pathway, and by terminating them through subsequent activation of the indirect pathway. Evidence for a role of the basal ganglia in such movement scaling was demonstrated in studies of the activity of pallidal neurons in monkeys trained to perform movements of different amplitudes [22].

An alternative model, first proposed by Denny-Brown, is that the basal ganglia act as a 'clearing house,' selecting the most appropriate action for a given situation. This view was incorporated by Kemp and Powel into their model (see above). A related concept was proposed by Albin, Young and Penney, who suggested that the basal ganglia act to select which movements should be carried out in response to competing sensory stimuli and to suppress unwanted movements [13]. This model was further developed by Mink, suggesting that the selection of specific movements involved activation of the direct pathway, while the inhibition of competing movements would involve activation of the indirect pathway, with the latter supplying a blanket inhibition in GPi out of which the direct pathway carved the intended movement [23].

A problem with these 'focusing' hypotheses is that the relatively slow conduction along the indirect pathway, as compared to that in the direct pathway, would result in premature activation of the 'focus' compared to the inhibition of competing movements. This problem was addressed by subsequent authors [24], invoking a non-striatal route for cortical inputs to reach the basal ganglia, the so-called 'hyperdirect' cortico-subthalamic pathway. Rapid activation of the STN–GPi route via the hyperdirect pathway would generate an inhibitory 'surround' on which a 'focus' could be placed to activate specific movements.

A major argument against the focusing hypothesis is that basal ganglia neuronal activity changes, even those in the STN, in relation to the onset of limb movement are too late to have a significant role in focusing, and by the fact that widespread activation of pallidal neurons that would serve a breaking function during a motor act have not been found. Furthermore, while both forms of the focusing hypothesis are based on the idea that the projections from the STN to the GPi are diffuse, in order to provide the postulated surround inhibition [25], more recent studies in primates showed that the projections within the indirect pathway are highly topographic [26]. Finally, it is difficult to understand why lesions of the STN or GPi in humans and nonhuman primates do not produce significant impairment of movement or result in postural difficulties, if the basal ganglia are assigned a role in movement initiation and postural control.

One of the obvious difficulties with the scaling or focusing hypotheses is that they require an active role of the basal ganglia in the selection process, while the evidence suggests that the basal ganglia modules are strongly directly tied to their specific cortical inputs. It would, therefore, seem most logical that action selection, focusing or scaling are primarily cortical rather than basal ganglia processes, and that the basal ganglia do not play a role in the initiation or selection of movement, but rather in the training or conditioning of the cortical modules.

A yet more recent attempt to assign a specific role to the direct/indirect pathway architecture is that the basal ganglia may serve a role in response inhibition [27]. For example, for eye movements, it has been suggested that the STN may play a role in inhibiting automatic eye movements, and switching to voluntary eye movements [28]. While physiologic studies of eye movements are consistent with a direct role of the basal ganglia in the initiation and control of eye movements, such is lacking for bodily movements. Studies by Houk and colleagues have, however, provided evidence for a role of GPi output in corrective movements. They argue for a role of the basal ganglia in both action selection and corrective movements [29].

In terms of functional interpretations, one of the shortcomings of the aforementioned models is that they are overly anatomic, lack physiologic support, and that basal ganglia activities cannot be simply described as the relay of 'excitatory' or 'inhibitory' inputs. An example to illustrate the last point is that many basal ganglia neurons and circuits autonomously produce oscillatory firing patterns due to intrinsic membrane properties. Furthermore, the simple models do not take into account more recent anatomical findings, such as the influence of thalamostriatal projections [30], extrastriatal actions of dopamine (e.g., [31]), or brain stem projections of the basal ganglia [32].

Based on the association between basal ganglia pathology and movement disorders, and on the results of single cell recordings in behaving primates, a direct role of the basal ganglia in motor control is often taken for granted. However, the finding that the timing of changes in neuronal activity in the basal ganglia in relation to movement onset lags that in cortex in reaction time tasks [33,34] and that lesions of the basal ganglia motor output (the sensorimotor territory of GPi) have little or no immediate or long term effects on posture, movement initiation, or movement execution in normal animals (and even improve movement in patients with Parkinson's disease), argues against a major role of the basal ganglia in the on-line control of movement. However, the fact that disturbances of neuronal activity solely within the basal ganglia, such as focal lesions or inactivation of the STN [35], injection of GABA-A receptor antagonists into GPe or striatum [36–38], and electrical stimulation of the primate putamen [39] can produce involuntary movements, suggest that abnormal activity in the basal ganglia and related brain areas can generate involuntary movements in abnormal states.

3. Disease-related dysfunction in specific basal ganglia circuits

When the direct/indirect circuit models were initially formulated, the implications for movement disorders was implicit [13,15]. Essential to these explanations was the differential effect of dopamine on the direct and indirect pathways. It was proposed that striatal neurons that give rise to the indirect pathway become hyperactive because of the loss of dopaminergic inhibition, resulting in reduced activity in GPe. This, in turn, was thought to disinhibit the STN–GPi axis, and lead to greater (inhibitory) GPi output to the thalamus. The change in basal ganglia output was postulated to be further aggravated by the loss of the facilitation dopamine on direct pathway neurons which led to disinhibition of GPi.

This 'rate model' linked the development of the hypokinetic features of Parkinson's disease with increased pallidal (inhibitory) output to the thalamus. As a corollary, dyskinesias (e.g., in hemiballismus), could be explained by a reduction in GPi inhibition of thalamocortical neurons, allowing unintended movements to proceed. Considerable support for these models came from studies of brain metabolism (see review in [40]), and neuronal recording studies in animal models of parkinsonism [41,42], and in animals and humans with dyskinesias (e.g., [43,44]). Additional support came from studies showing that lesions of GPi and STN are highly effective in treating bradykinesia, rigidity and tremor in animals with experimental parkinsonism (e.g., [45,46]) and humans with Parkinson's disease (e.g., [47,48]), and the finding that the hemiballismus produced by STN inactivation is accompanied by decreased GPi activity [35].

However, the rate model for PD cannot explain several key findings, for example, the finding that lesions of the motor thalamus [49] or GPe [50] do not result in bradykinesia or akinesia and that GPi lesions in parkinsonian patients do not result in dyskinesias. In place of the rate model, subsequent models emphasized the presence of abnormal firing patterns, such as bursts and oscillatory patterns in the basal ganglia

and abnormal synchronization [51]. The currently favored model ascribes parkinsonism to a disruption of normal cortical activities because of the excessive beta-band oscillations and a reduction in gamma-band oscillations throughout the motor circuit [51]. Although this model has experimental support from animal and human recordings, it, too, remains controversial. Thus, while recordings utilizing implanted DBS electrodes and local field potential recording in parkinsonian patients have demonstrated the presence of beta-band oscillations, and weak gamma oscillatory activity, both reversible by treatment with dopaminergic drugs, this has not been consistently demonstrated [52]. Furthermore, in animal studies, oscillatory firing patterns may emerge at a relatively late stage of dopamine depletion [53], after the development of parkinsonism, and that systemic dopamine receptor antagonists induce parkinsonism, but do not produce substantial oscillations in the basal ganglia and cortex [54]. These findings suggest that oscillatory activities may be present in advanced parkinsonism, but are not necessarily the primary cause of akinesia or bradykinesia.

4. Outlook

The anatomical and physiological models mentioned above have had a tremendous impact on our thinking about the basal ganglia and basal ganglia disorders and have stimulated research and the development of new therapeutic approaches.

Clearly some of the features and hypotheses related to models have stood the test of time. The modular arrangement of the basal ganglia–thalamocortical circuitry, the basic circuit model of the intrinsic connections between the basal ganglia, and the importance of dopamine release at regulating the transmission at specific synapses in the striatum are accepted. However, some of the details of the earlier pathophysiology models of basal ganglia diseases have fallen by the wayside, most likely because the anatomical models were too rigidly transformed into static functional models. The early view that the basal ganglia play a major role in movement initiation and execution is difficult to reconcile with data from both humans and monkey studies that are more compatible with a role in learning and habit formation than on-line motor control, but this remains an issue for further inquiry. There is a wealth of new anatomical and physiological data that needs to be incorporated into future versions of these models.

Additional anatomic and physiologic information is needed to understand to what extent the loops are 'closed'. In addition, we need a better understanding of the function of the cortico-thalamocortical loops, and of the way(s) by which basal ganglia and cerebellar output regulates them. Further clarification of the motor functions of the basal ganglia is a significant challenge. Furthermore, the role of the recently identified connections between the basal ganglia and cerebellum needs to be defined. New models also need to incorporate the intrinsic processing within the basal ganglia nuclei, including the significance of the patch/matrix organization of the striatum, and the role of interneuronal processing in the striatum. Finally, future models need to focus more on the functions of the individual circuits and subcircuits.

Conflict of interests

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