Functional architecture of basal ganglia circuits: neural substrates of parallel processing

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Concepts of basal ganglia organization have changed markedly over the past decades, due to significant advances in our understanding of the anatomy, physiology, and pharmacology of these structures. Independent evidence from each of these fields has reinforced a growing perception that the functional architecture of the basal ganglia is essentially parallel in nature, regardless of the perspective from which these structures are viewed. This represents a significant departure from earlier concepts of basal ganglia organization, which generally emphasized the serial aspects of their connectivity. Current evidence suggests that the basal ganglia are organized into several structurally and functionally distinct 'circuits' that link cortex, basal ganglia and thalamus, with each circuit focused on a different portion of the frontal lobe. In this review, Garrett Alexander and Michael Crutcher, using the basal ganglia 'motor' circuit as the principal example, discuss recent evidence indicating that a parallel functional architecture may also be characteristic of the organization within each individual circuit.

Past views of basal ganglia organization were strongly influenced by the progressive reduction in nuclear volume and apparent 'funneling' that is evident along the pathways that lead from cerebral cortex through the basal ganglia, to the ventromedial thalamus. Because of these large-scale anatomical features, the prevailing view was that the basal ganglia served essentially to integrate converging influences from cortical 'association' and 'sensorimotor' areas during their passage through the basal ganglia to common thalamic target zones. It was also widely believed that these same basal ganglia recipient zones within the ventrolateral thalamus received ascending, convergent inputs from the cerebral cortex and returned their own projections exclusively to primary motor cortex.

Recent findings, however, are at variance with each of these views. Not only has it been shown that basal ganglia and cerebellar projections are directed to entirely separate target zones within the ventrolateral thalamus1,2, but there is now also considerable evidence that the respective influences from cortical association and sensorimotor regions remain segregated throughout the partially closed, re-entrant pathways (circuits) that link cortex, basal ganglia and thalamus1,2. Moreover, the combined output of these circuits has been found to project not simply to primary motor cortex, but to virtually the entire frontal lobe. Indeed, the available evidence suggests that there are at least five such basal ganglia-thalamocortical circuits, which, while organized in parallel, remain largely segregated from one another, both structurally and functionally3. Each of these circuits is thought to engage separate (though often contiguous) regions of the basal ganglia and thalamus, and the output of each appears to be centered on a different part of the frontal lobe (Fig. 1). The 'motor' circuit is focused on the precentral motor fields, the 'oculomotor' circuit on the frontoparietal and supplementary eye fields, the two 'prefrontal' circuits on the dorsolateral prefrontal and lateral orbitofrontal cortex, respectively, and the 'limbic' circuit on the anterior cingulate and medial orbitofrontal cortex4. According to this more recent view, the basal ganglia appear to be capable of concurrent participation in a number of separate functions (including skeletonmotor, oculo-motor, cognitive and 'limbic' processes), due to the parallel structure of the individual basal ganglia-thalamocortical circuits5.

Here, we do not attempt to cover the extensive evidence of structural and functional segregation among the various circuits. Reviews of this topic are available elsewhere1,3. Instead, we focus on the question of whether a parallel functional architecture is also evident within the individual circuits. We begin by outlining some of the basic properties that are thought to be characteristic of the basal ganglia-thalamocortical circuits, including the two parallel pathways within each circuit that appear to have opposite influences on the basal ganglia output nuclei. We then consider in more detail the motor circuit, which to date has been studied the most extensively to illustrate certain additional features that are also indicative of an intrinsically parallel organization, features that have been either shown or predicted to occur in other circuits. Comparable discussions of the oculomotor, prefrontal and 'limbic' circuits occur elsewhere3.

Fig. 1. Frontal lobe targets of basal ganglia output. Schematic illustration of the cortical areas that receive the output of the separate basal ganglia-thalamocortical circuits. Abbreviations: ACA, anterior cingulate area; DLPC, dorsolateral prefrontal cortex; FEF, frontal eye field; LOFC, lateral orbitofrontal cortex; MC, primary motor cortex; MOVC, medial orbitofrontal cortex; PMC, premotor cortex; SFE, supplementary eye field; SMA, supplementary motor area.

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Basic circuit organization

Certain features shared by all of the basal ganglia-globus pallidus circuits are indicated schematically in Fig. 2. In each case, specific cortical areas send excitatory, glutamatergic projections to selected portions of the striatum (comprising the caudate nucleus, putamen, and ventral striatum), which is generally thought to represent the ‘input’ stage of the basal ganglia. By virtue of their high rates of spontaneous discharge, the basal ganglia output nuclei (the internal segment of the globus pallidus, GPi; substantia nigra pars reticulata; SNr; and ventral pallidum) exert a tonic, GABA-mediated, inhibitory effect on their target nuclei in the thalamus[8]. Within each circuit, this inhibitory outflow appears to be differentially modulated by two opposing but parallel pathways that pass from the striatum to the basal ganglia output nuclei.

Each circuit includes a ‘direct’ pathway to the output nuclei, which arises from inhibitory striatal neurons that contain both GABA and substance P[9]. Activation of this pathway tends to disinhibit the thalamic stage of the circuit[10]. Each circuit also includes an ‘indirect’ pathway, which passes first to the external segment of the globus pallidus (GPen) via striatal projection neurons that contain both GABA and enkephalin[10], then from GPen to the subthalamic nucleus via a purely GABergic pathway, and finally to the output nuclei via an excitatory, probably glutamatergic[11], projection from the subthalamic nucleus. The high spontaneous discharge rate of most GPen neurons exerts a tonic inhibitory influence on the subthalamic nucleus. Activation of the inhibitory GABA-ergic projection from the subthalamus to the striatum tends to suppress the activity of GABAergic neurons and thereby disinhibit the subthalamic nucleus, increasing the excitatory drive on the output nuclei and increasing the inhibition of their efficient targets within the thalamus. The two striatal effector systems of each circuit thus appear to have opposing effects upon the basal ganglia output nuclei and, accordingly, upon the thalamic targets of basal ganglia outflow.

During the execution of specific motor acts, movement-related neurons within the basal ganglia output nuclei may show either phasic increases or phasic decreases in their normally high rates of spontaneous discharge[12,13]. There is mounting evidence that phasic decreases in GPI/SNr discharge play a crucial role in motor control by disinhibiting the retrolateral thalamus and thereby gates or facilitating cortically initiated movements (via excitatory thalamo-cortical connections), and that phasic increases in GPI/SNr discharge may have the opposite effect[12,13,14,15]. As yet, however, little is known about how inputs from the direct and indirect pathways may interact to control basal ganglia output at the level of individual neurons within GPI and SNr. One possibility is that both the direct (GABAergic substance P) and the indirect (glutamatergic) inputs to the basal ganglia output nuclei that are activated selectively and concurrently in association with a particular cortically initiated movement may be directed to the same set of GPI/SNr neurons. With this arrangement, the inputs from the indirect pathway might be seen as either ‘braking’ or ‘smoothing’ the same cortically initiated motor pattern that was being reinforced by the direct pathway. Alternatively,

Fig. 2. Schematic diagram of the circuitry and neurotransmitters of the basal ganglia-thalamocortical circuitry, indicating the parallel ‘direct’ and ‘indirect’ pathways from the external to the basal ganglia output nuclei. Inhibitory neurons are shown as filled symbols, excitatory neurons as open symbols. Abbreviations: DA, dopamine; enk, enkephalin; GABA, γ-aminobutyric acid; GPen, external segment of globus pallidus; GPi, internal segment of globus pallidus; glu, glutamate; PPN, pedunculopontine nucleus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; subP, substance P; STN, subthalamic nucleus; Thal, thalamus.

the direct and indirect inputs associated with a particular motor pattern could be directed to separate sets of GPI/SNr neurons. In this configuration, the motor circuit might be seen as playing a dual role in the modulation of motor patterns initiated at cortical levels by both reinforcing the currently selected patterns via the direct pathway and suppressing potentially conflicting patterns via the indirect pathway. Overall, this could result in the focusing of neural activity underlying each cortically initiated movement in a fashion analogous to the "inhibitory surround" seen in various sensory systems.

The role of dopamine within the basal ganglia appears to be complex, and many issues remain unresolved. However, there is recent evidence that the nigrostriatal dopamine projections exert contrasting effects on the direct and indirect striatofugal pathways. Dopaminergic inputs appear to have a net excitatory effect on striatal neurons that send GABAergic substance P projections to the basal ganglia output nuclei (via the direct pathway), and a net inhibitory
effect on those that send GABA-NSNepalpamin projections to GPc (via the indirect pathway)21-23. Thus, in effect, the overall influence of dopamine within the striatum may be to reinforce any cortico-striatal activation of a particular basal ganglia-thalamocortical circuit by both facilitating conduction through that circuit's direct pathway (which has a net excitatory effect on the thalamic nuclei) and suppressing conduction through the indirect pathway (which has a net inhibitory effect on the thalamic nuclei).

The striatal circuitry depicted in Fig. 2B, is, of course, greatly oversimplified. We have indicated a few of the feedback mechanisms associated with the basal ganglia-thalamocortical circuits, including the thalamo-striatal projections and the reciprocal projections between the basal ganglia output nuclei and the pedunculopontine nucleus24-26. However, we do not show a variety of structural details, such as the intrinsic feedback connections within each nucleus, and the projections returned from the subthalamic nucleus to the striatum.

In cats and rodents, GPc has been shown to send substantial projections to the reticular nucleus of the thalamus, which could provide a route for conveying basal ganglia influences to many, if not all, thalamic nuclei, instead of just the few that receive direct projections from either GPe, SNR or the ventral pallidum27-29. In primates, however, a projection from GPe to the thalamus does not appear to exist27-28.

We have also omitted from the circuit diagram several neurotransmitter systems that are believed to influence striatal functions but whose actual roles in circuit operations remain poorly understood. One of these is acetylcholine, whose clinical effects in various movement disorders (especially Parkinson's disease) are generally antagonistic to those of dopamine. There is some evidence that these antagonistic effects might be mediated by excitatory cholinergic inputs (presumably from the large, cholinergic, transferrase-positive, striatal interneurons30-32) directed preferentially to the GABA-NSNepalpamin neurons of the direct pathway30-32.

It should be mentioned that within the limbic circuit the demarcation of the direct (GABA-substance P) and indirect (GABA-NSNepalpamin) pathway is not as clear as it is for the other circuits. Although it receives projections from both the GABA-substance P and the GABA-NSNepalpamin neurons of the ventral striatum, the limbic circuit's ventral pallidum is not structurally differentiated in a manner comparable to that of the internal and external segments of the globus pallidus.

We have not discussed the patch/matrix compartmentalization within the basal ganglia. As this topic is covered in the article by Graybiel that also appears in this issue. However, it is likely that the patch/matrix system, which appears to be superimposed upon other levels of functional differentiation, and between the different basal ganglia-thalamocortical circuits, represents an additional example of the phylogenetically parallel nature of basal ganglia architecture. The motor circuit

In primates, the inputs to the basal ganglia portion of the motor circuit are focused principally on the putamen (Fig. 3). This part of the striatum receives topographic projections from the motor cortex and from at least two motor areas, including the arcuate premotor area (APA) and the supplementary motor area (SMA)34-37. The putamen also receives topographic projections from somatosensory cortex34-38. These projections result in a somatotopic organization that consists of a dorso-lateral zone in which the leg is represented, a ventromedial orbital region, and a territory in between in which there is representation of the arm34,36,39. Each of these representations extends along virtually the entire rostro-caudal axis of the putamen.

While the 'arm region' of the putamen receives projections from the respective arm representations within the SMA, primary motor cortex and the APA34,35, a recent investigation using double anterograde labeling has shown that the terminal fields of these different projections, though contiguous, are essentially non-overlapping34. These findings raise the possibility, as yet untested, that such segregation may be maintained at subsequent stages in the pallidum and thalamus. If so, it would mean that there may be separate (e.g. SMA- and motor cortex-specific) sub-channels within each of the somatotop-
The somatotopic organization of the motor circuit is illustrated in Figure 4. This diagram shows the distribution of different motor functions across the cerebral cortex. The arrows indicate the topographically organized pathways that link the respective areas at different stages of the circuit. Abbreviations: SMA, supplementary motor area; VPA, nucleus ventralis anterior pars parvocellularis; VLo, nucleus ventralis lateralis pars oralis.

Changes in neuronal discharge in relation to the onset of rapid, stimulus-triggered limb movements tend, on average, to occur somewhat earlier at cortical than at subcortical stages of the motor circuit, although there is considerable overlap among the different distributions. This suggests that some degree of serial processing within the basal ganglia-thalamocortical circuits, and the possibility that the activity within these circuits might at least be initiated at cortical levels. For the duration of the burst of movement-related discharge, however, there is essentially complete temporal overlap of activity at cortical and subcortical stages of the circuit, suggesting that much of the motor processing proceeds concurrently, i.e. in parallel, at these different stations.

Recent findings indicate that the motor circuit may be involved not only in the execution of movements, but also in the preparation for movement. Studies in primates have shown that the precentral motor fields, including premotor cortex, SMA and motor cortex, each contain neurons that show striking changes in discharge rate following presentation of an instructional stimulus that specifies the direction of an upcoming (stimulus-triggered) limb movement. These directionally specific, instruction-dependent changes in activity are characteristic of the preparatory aspects of motor control referred to as 'motor set'. Similar directionally selective preparatory activity has been documented within the parietam162, 163. The fact that individual neurons within these structures tend to exhibit either preparatory (set-related) or movement-related responses,
rather than combinations of the two, suggested the possibility that preparatory and execution-related aspects of motor control might be mediated by separate sub-channels within each of the somatotopic channels of the motor circuits.24-26

There is also evidence to indicate that during both the preparation and execution of limb movements several different aspects of motor processing may be carried out simultaneously, that is, in parallel, at different points within the motor circuit. The problem of controlling goal-directed limb movements can be divided into a sequence of analytically defined "levels" of motor processing that are required to translate the spatial characteristics of the target or goal of the movement into an appropriate pattern of muscle activation.28,29,30 Whether the brain uses such a sequential approach to motor processing is not known. Recently, we addressed this issue by examining neuronal activity at three different stations within the motor circuit in monkeys trained to perform a set of behavioral paradigms that disassociated several distinct functional "levels" of motor processing.31-33 Each of the structures examined (SMA, motor cortex and putamen) was found to contain separate populations of neurons that discharged selectively in relation to (1) target-level variables (reflecting the location of the target in space), (2) trajectory/kinematics-level variables (reflecting the direction of limb movement, independent of muscle pattern or limb dynamics), or (3) dynamic/muscle-level variables (reflecting movement force and/or muscle pattern). The neural representations of these different levels of motor processing were distributed across multiple structures within the circuit, and the timing of neuronal activity related to the various processing levels was found to be largely concurrent.28,29,30 These new results suggest that within each of the somatotopic channels of the motor circuit (leg, arm, orofacial) there may well be a deeper level of organization represented by functionally specific sub-channels that encode selectively, but in parallel, information about each disparate motor behavioral variable as target location, limb kinematics and muscle pattern.

Neural substrates of functional integration

From the standpoint of information processing, it would make little sense for the basal ganglia-thalamocortical circuitry simply to relay unprocessed information around closed and completely isolated loops that did not permit any form of functional "integration." However, from the available evidence it seems that structural convergence and functional integration are more likely to occur within than between the separate basal ganglia-thalamocortical circuits.28-30 This is underscored by the fact that even within the motor circuit, there are separate somatotopic channels for the control of leg, arm and orofacial movements, and that the recent evidence suggesting that within each of these somatotopic channels there may be further functional subdivisions ("sub-channels") that selectively subserve different aspects of motor processing (and possibly process information derived from each of the different precentral motor fields separately, within additional sub-channels).

Given the evidence of such strict maintenance of structural segregation and functional specificity within the basal ganglia-thalamocortical circuits, it may be necessary to re-evaluate conventional expectations of how functional integration might be implemented within these networks. It is conceivable, for example, that the functional integration that is widely assumed to occur within these circuits may prove to be no less upon the spatial convergence of functionally disparate pathways than upon the temporal coincidence of processing within pathways whose substructure segregation is rather strictly maintained. At the coarsest level of analysis, this type of functional integration, based on temporally coincident processing within structurally segregated networks, might be exemplified by the simultaneous processing of information relating to coordinated basal and limb movements within the respective domains of the motor and oculomotor circuits. Of course a major advantage of this type of functional architecture would be its capacity to support concurrent or parallel processing of a potentially vast number of neo- and behavioral variables.

Concluding remarks

There is now a wealth of evidence, from a variety of experimental perspectives, suggesting that the functional organization of basal ganglia circuitry reflects a fundamentally parallel form of neural architecture. We have located here on the basal ganglia motor circuit, just one of a family of basal ganglia-thalamocortical circuits, to illustrate the broad range of evidence indicating that even within the different circuits the functional architecture is essentially parallel in nature. Additional investigations will be required to determine the extent to which certain elements of parallel structure and processing seen within the motor circuit may also be represented within the other basal ganglia-thalamocortical circuits. Doubtless, certain aspects of these functional relationships will prove to be unique to each circuit. Nevertheless, from the current evidence it would seem reasonable to view this family of circuits as having a unified role in modulating the operations of the entire frontal lobe, influencing in parallel, and by common mechanisms, such diverse "frontal lobe" processes as the maintenance and switching of various behavioral sets (via the prefrontal and limbic circuits) and the planning and execution of limb and visuomotor movements (via the motor and oculomotor circuits).31-33

Selected references
