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 decade, 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 ventrolateral 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 cerebellum and returned their own projections exclusively to primary motor cortex.

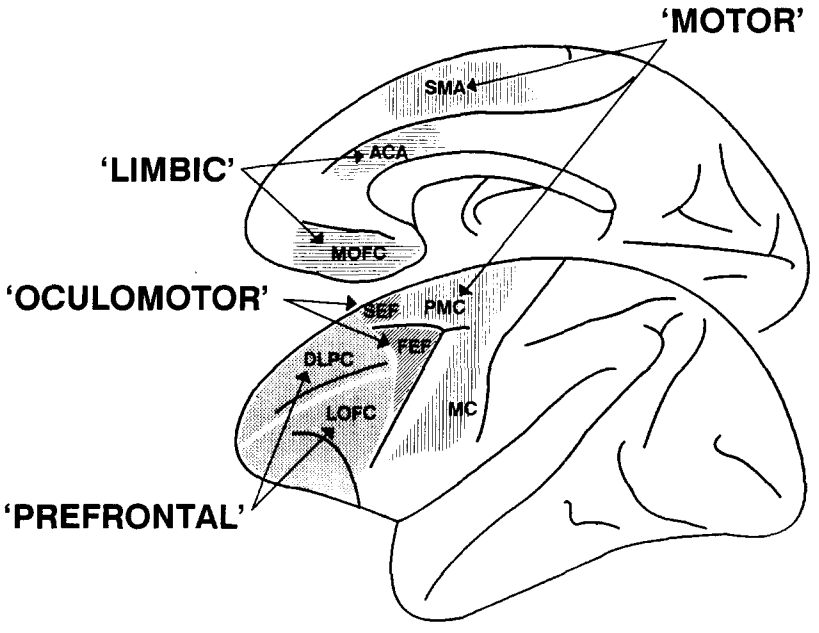

Fig. 1. *Frontal lobe targets of basal ganglia output. Schematic illustration of the cortical areas that receive the output of the separate basal ganglia–thalamocortical circuits. Abbreviations: ACA, anterior cingulate area; DLPC, dorsolateral prefrontal cortex; FEF, frontal eye field; LOFC, lateral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

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 thalamus[1,2], 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 thalamus[3]. 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 functionally[4]. 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 frontal 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 cortex[5]. According to this more recent view, the basal ganglia appear to be capable of concurrent participation in a number of separate functions (including skeletomotor, oculomotor, cognitive and 'limbic' processes), due to the parallel structure of the individual basal ganglia–thalamocortical circuitry[5].

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 elsewhere[4,5]. 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 common to each of the basal ganglia–thalamocortical circuits, including the two parallel pathways within each circuit that appear to have opposing 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 have analogous representations within the other circuits. Comparable discussions of the oculomotor, prefrontal and limbic circuits occur elsewhere[5].

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Basic circuit organization

Certain features shared by all of the basal ganglia–thalamocortical circuits are indicated schematically in Fig. 2. In each case, specific cortical areas send excitatory, glutamatergic projections[6,7] 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[3,8]. 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[9–11]. 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 efferents that contain both GABA and substance P[12,13]. Activation of this pathway tends to disinhibit the thalamic stage of the circuit[10,11]. Each circuit also includes an 'indirect' pathway, which passes first to the external segment of the globus pallidus (GPe) via striatal projection neurons that contain both GABA and enkephalin[13], then from GPe to the subthalamic nucleus via a purely GABAergic pathway, and finally to the output nuclei via an excitatory, probably glutamatergic[14,15], projection from the subthalamic nucleus. The high spontaneous discharge rate of most GPe neurons exerts a tonic inhibitory influence on the subthalamic nucleus. Activation of the inhibitory GABA/enkephalin projection from the striatum tends to suppress the activity of GPe neurons and thereby disinhibit the subthalamic nucleus, increasing the excitatory drive on the output nuclei and increasing the inhibition of their efferent targets within the thalamus. The two striatal efferent 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[16–18]. There is mounting evidence that phasic *decreases* in GPi/SNr discharge play a crucial role in motor control by disinhibiting the ventrolateral thalamus and thereby gating or facilitating cortically initiated movements (via excitatory thalamocortical connections), and that phasic *increases* in GPi/SNr discharge may have the opposite effect[5,12,19,20]. 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' (GABA/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, 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 pattern 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.

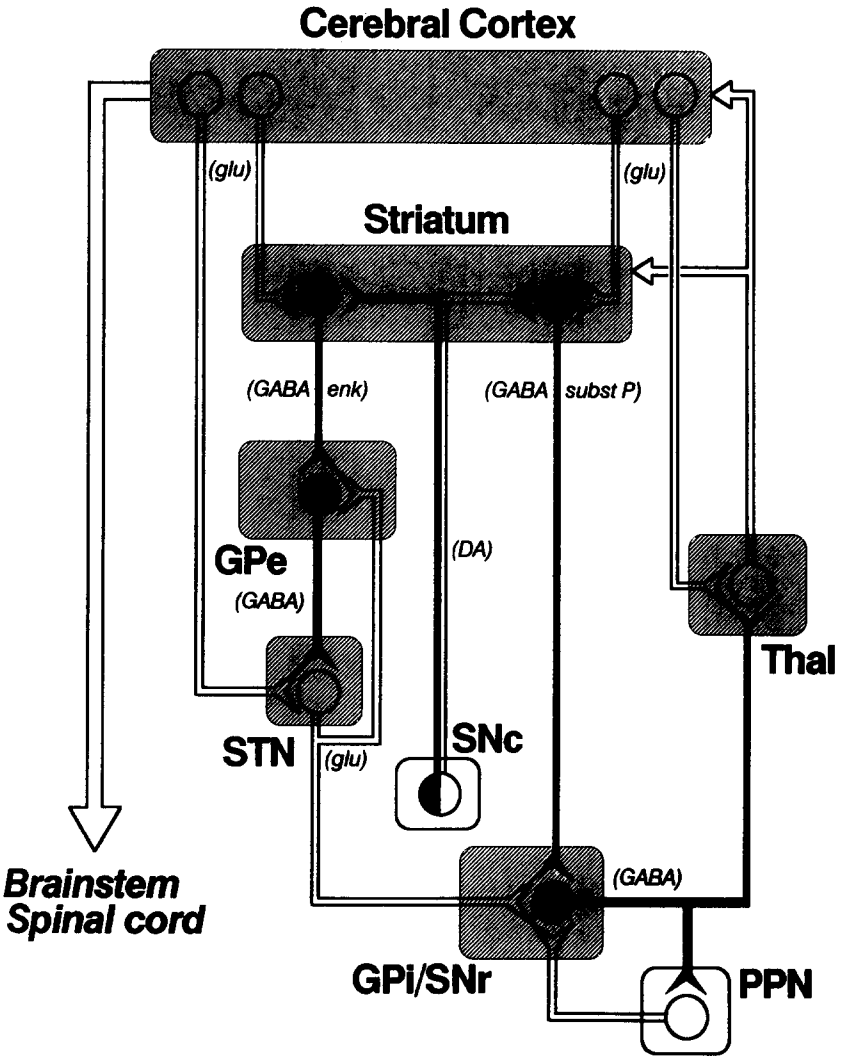

Fig. 2. *Schematic diagram of the circuitry and neurotransmitters of the basal ganglia–thalamocortical circuitry, indicating the parallel 'direct' and 'indirect' pathways from the striatum to the basal ganglia output nuclei. Inhibitory neurons are shown as filled symbols, excitatory neurons as open symbols. Abbreviations: DA, dopamine; enk, enkephalin; GABA, γ-aminobutyric acid; GPe, 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; subst P, substance P; STN, subthalamic nucleus; Thal, thalamus.*

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 GABA/substance P projections to the basal ganglia output nuclei (via the direct pathway), and a net inhibitory

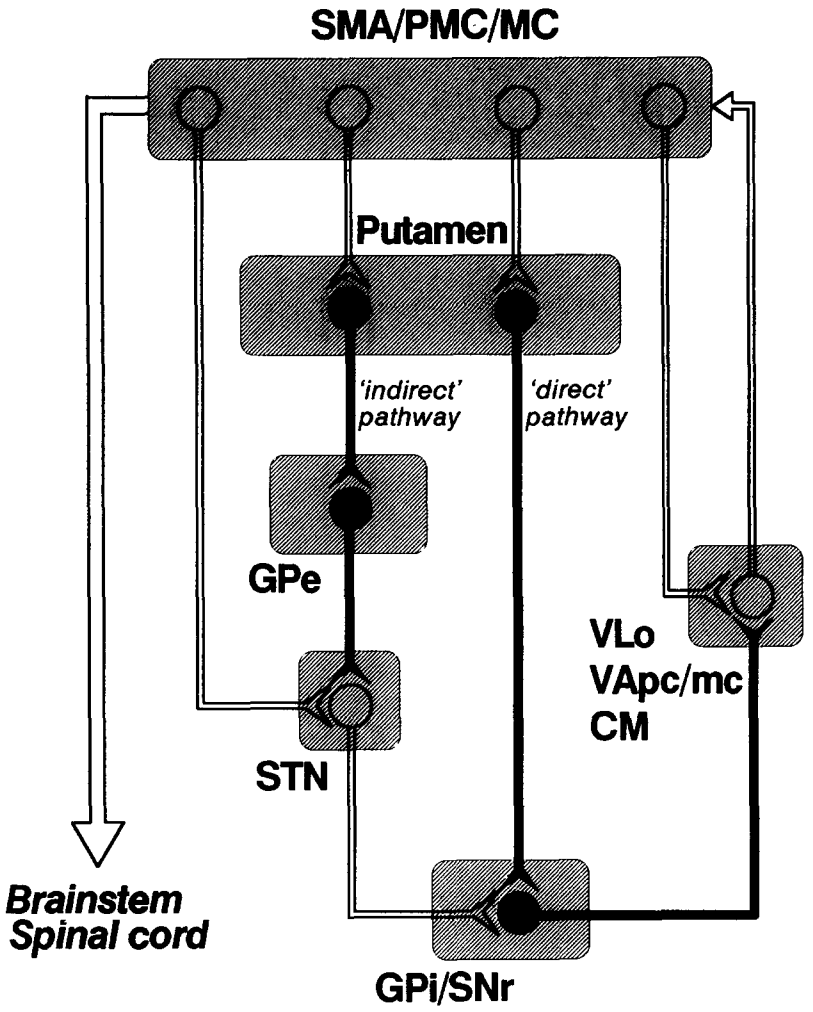

Fig. 3. *Simplified diagram of the 'motor' circuit. The cortical areas shown projecting to the putamen include only the 'closed loop' portions of the motor circuit. Additional 'open loop' corticostriatal inputs to the motor circuit arise from the arcuate premotor area and somatosensory cortex. Inhibitory neurons are filled, excitatory neurons are open. Abbreviations: CM, centromedian nucleus; GPe, external segment of globus pallidus; GPi, internal segment of globus pallidus; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; VAmc, nucleus ventralis anterior pars magnocellularis; VApc, nucleus ventralis anterior pars parvocellularis; VLo, nucleus ventralis lateralis pars oralis.*

effect on those that send GABA/enkephalin projections to GPe (via the indirect pathway)[21–24]. Thus, in effect, the overall influence of dopamine within the striatum may be to reinforce any cortically initiated 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 thalamus) and suppressing conduction through the indirect pathway (which has a net inhibitory effect on the thalamus).

The scheme depicted in Fig. 2 is, of course, greatly oversimplified. We have indicated a few of the feedback mechanisms associated with the basal ganglia–thalamocortical circuits, including the thalamostriatal projections and the reciprocal projections between the basal ganglia output nuclei and the pedunculopontine nucleus[25,26]. 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, GPe 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 GPi, SNr or the ventral pallidum[27,28]. In primates, however, a projection from GPe to the thalamus does not appear to exist[29–32].

We have also omitted from the circuit diagram several neurotransmitter systems that are believed to influence striatal operations 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, choline acetyltransferase-positive, striatal interneurons[33]) directed preferentially to the GABA/enkephalin neurons of the indirect pathway[19,22].

It should be mentioned that within the limbic circuit the demarcation of the direct (GABA/substance P) and indirect (GABA/enkephalin) pathways is not as clear as it is for the other circuits. Although it receives projections from both the GABA/substance P and the GABA/enkephalin 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 lines of functional demarcation within and between the different basal ganglia–thalamocortical circuits, represents an additional example of the inherently 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 primary motor cortex and from at least two premotor areas, including the arcuate premotor area (APA) and the supplementary motor area (SMA)[34–37]. The putamen also receives topographic projections from somatosensory cortex[34,38]. These projections result in a somatotopic organization that consists of a dorsolateral zone in which the leg is represented, a ventromedial orofacial region, and a territory in between in which there is representation of the arm[35,39,40]. Each of these representations extends along virtually the entire rostrocaudal 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 APA[35,38], a recent investigation using double anterograde labeling has shown that the terminal fields of these different projections, though contiguous, are essentially non-overlapping[41]. These findings raise the possibility, as yet untested, that such segregation may be maintained at subsequent stations 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-

ically defined (leg, arm, orofacial) channels of the motor circuit.

The putamen projects topographically to specific portions of GPe, GPi and SNr[42–44]. In turn, the respective 'motor' portions of GPi and SNr send topographic projections to specific thalamic nuclei, including the VLo (nucleus ventralis lateralis pars oralis), lateral VApc (nucleus ventralis anterior pars parvocellularis), lateral VAmc (nucleus ventralis anterior pars magnocellularis) and the centromedian nucleus[25,29,30,32,45]. The motor circuit is closed by means of the thalamocortical projections from VLo and lateral VAmc to the SMA[46–49], from lateral VApc (as well as VLo) to premotor cortex (exclusive of the APA, which appears to receive only cerebellar influences via thalamic area X)[48,50], and from VLo and CM to motor cortex[46,47,49,50].

It has been suggested that the functional specificity of information processing within the globus pallidus might be degraded as a result of the massive spatial convergence of the striatopallidal projection, which cuts orthogonally across the large, disc-like dendritic fields of individual pallidal neurons[51]. In fact, however, neurophysiological studies in behaving primates have revealed a pronounced degree of functional specificity and somatotopic coding among neurons at all stages of the motor circuit[39,52–56], and both anatomical and physiological studies have confirmed that each part of the circuit is somatotopically organized (Fig. 4). Thus, while it might be reasonable to expect there to be some degree of functional integration within the motor circuit, any such integrative process appears not to have seriously compromised either the functional 'tuning' of individual neurons within the circuit or the functional segregation of that circuit's parallel somatotopic channels.

The functional specificity of neurons within the motor circuit has been demonstrated in a variety of ways. For example, neuronal activity within the circuit has been examined in monkeys performing motor tasks that dissociated the direction of limb movement from the pattern of muscle activity. At cortical, striatal and pallidal stages of the circuit, the activity of substantial proportions of movement-related neurons has been found to depend upon the direction of limb movement independent of the associated pattern of muscle activity. Within the SMA, motor cortex, putamen, GPi and GPe, such 'directional' cells were found to comprise from 30 to 50% of the movement-related neurons, all of which showed sharply delineated somatotopic features[18,53,57]. Other movement-related cells that showed 'muscle-like' specificity were also found in significant numbers within each of these areas.

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[17,53,57–59]. These findings suggest some degree of serial processing within the basal ganglia–thalamocortical circuits, and raise the possibility that much of 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[57].

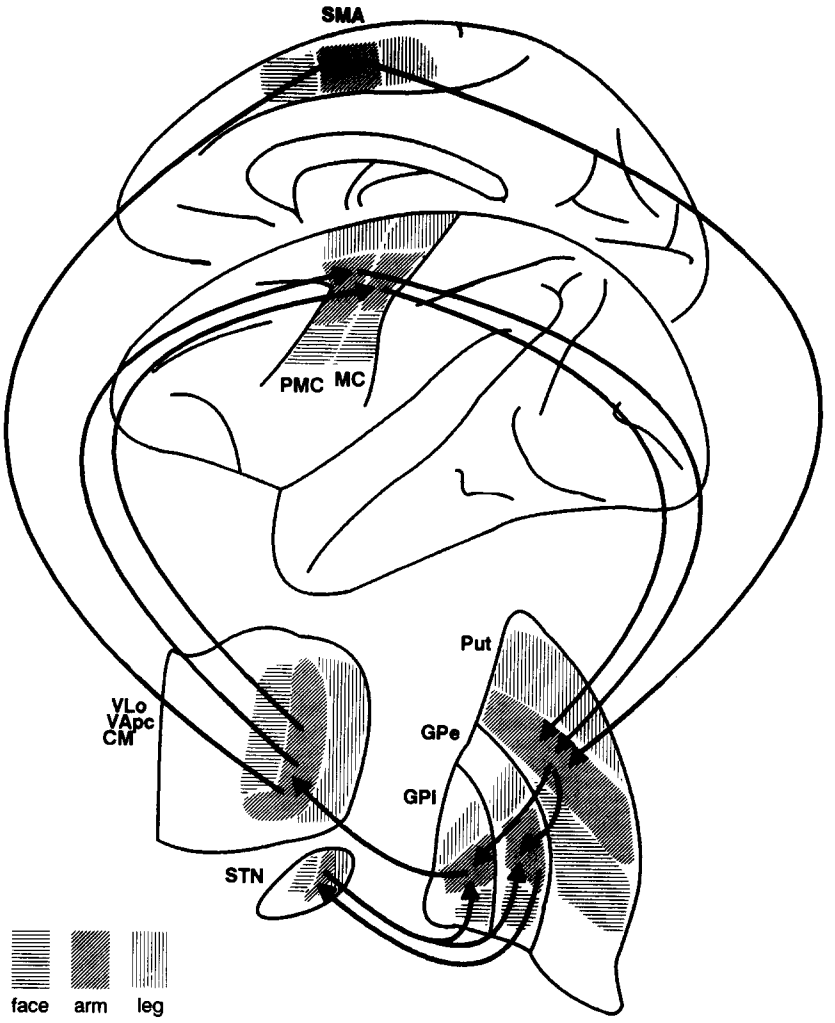

Fig. 4. *Somatotopic organization of the 'motor' circuit. Somatotopic subdivisions of each structure are indicated by differential shading. The arrows indicate the topographically organized pathways that link the respective 'arm' representations at different stages of the circuit. Abbreviations: CM, centromedian nucleus; GPe, external segment of globus pallidus; GPi, internal segment of globus pallidus; MC, primary motor cortex; PMC, premotor cortex exclusive of the arcuate premotor area; Put, putamen; SMA, supplementary motor area; VApc, nucleus ventralis anterior pars parvocellularis; VLo, nucleus ventralis lateralis pars oralis.*

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[52,58,60–64]. These directionally specific, instruction-dependent changes in activity are characteristically sustained until the occurrence of the movement-triggering stimulus, and appear to represent a neural correlate of one of the preparatory aspects of motor control referred to as 'motor set'. Similar directionally selective preparatory activity has been documented within the putamen[52,65]. 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 circuit[4,52,65].

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 activations[66]. 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 dissociated several distinct functional 'levels' of motor processing[52,57,67]. 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) dynamics/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[52,57,67]. 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 such disparate motor behavioral variables 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[4,5]. 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 by 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 based less upon the spatial convergence of functionally disparate pathways than upon the temporal coincidence of processing within pathways whose functional 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 hand and eye 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 capability to support concurrent or parallel processing of a potentially vast number of neurobehavioral 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 focused 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 their respective functional architectures 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 eye movements (via the motor and oculomotor circuits)[4,5].

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