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PARALLEL ORGANIZATION OF FUNCTIONALLY SEGREGATED CIRCUITS LINKING BASAL GANGLIA AND CORTEX*

Garrett E. Alexander

Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205

Mahlon R. DeLong

Departments of Neurology and Neuroscience, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205

Peter L. Strick

Research Service, Veterans Administration Medical Center, Departments of Neurosurgery and Physiology, State University of New York–Upstate Medical Center, Syracuse, New York 13210

INTRODUCTION

Information about the basal ganglia has accumulated at a prodigious pace over the past decade, necessitating major revisions in our concepts of the structural and functional organization of these nuclei. From earlier data it had appeared that the basal ganglia served primarily to integrate diverse inputs from the entire cerebral cortex and to "funnel" these influences, via the ventrolateral thalamus, to the motor cortex (Allen & Tsukahara 1974, Evarts & Thach 1969, Kemp & Powell 1971). In particular, the basal

ganglia were thought to provide a route whereby influences from the cortical association areas might be transmitted to the motor cortex and thereby participate in the initiation and control of movement.

Subsequent anatomical and physiological findings led to a revised view that stressed the apparent maintained segregation of influences from the sensorimotor and association cortices through the basal ganglia–thalamocortical pathways (DeLong & Georgopoulos 1981). On the basis of the then existing data, it was suggested that there might be two distinct loops through the basal ganglia: (*a*) a "motor" loop passing largely through the putamen, which received inputs from sensorimotor cortex and whose influences were ultimately transmitted to certain premotor areas, and (*b*) an "association" (or "complex") loop passing through the caudate nucleus, which received input from the association areas and whose influences were ultimately returned to portions of the prefrontal cortex (DeLong & Georgopoulos 1981, DeLong et al 1983b).

Recent anatomical and physiological findings have further substantiated the concept of segregated basal ganglia–thalamocortical pathways, and reinforced the general principle that basal ganglia influences are transmitted only to restricted portions of the frontal lobe (even though the striatum receives projections from nearly the entire neocortex). It has been shown, for example, that the thalamocortical portion of the "motor" circuit terminates largely within a restricted premotor region, the supplementary motor area (Schell & Strick 1984), while the corticostriate inputs to this circuit include projections not only from the supplementary motor area but from motor, arcuate premotor, and somatosensory cortex as well (Kunzle 1975, 1977, 1978). Using the "motor" circuit as a model, we have reexamined the available data on other portions of the basal ganglia–thalamocortical pathways and found that the evidence strongly suggests the existence of at least four additional circuits organized in parallel with the "motor" circuit. In the discussion that follows, we review some of the anatomic and physiologic features of the "motor circuit," as well as the data that support the existence of the other proposed parallel circuits, which we have designated the "oculomotor," the "dorsolateral prefrontal," the "lateral orbitofrontal," and the "anterior cingulate," respectively. Each of these five basal ganglia–thalamocortical circuits appears to be centered upon a separate part of the frontal lobe, as indicated in Figure 1.

This list of basal ganglia–thalamocortical circuits is not intended to be exhaustive. In fact, if the conclusions suggested in this review are valid, future investigations might be expected to disclose not only further details (or the need for revisions) of these five circuits, but perhaps also the existence of additional parallel circuits whose identification is currently precluded by a paucity of data.

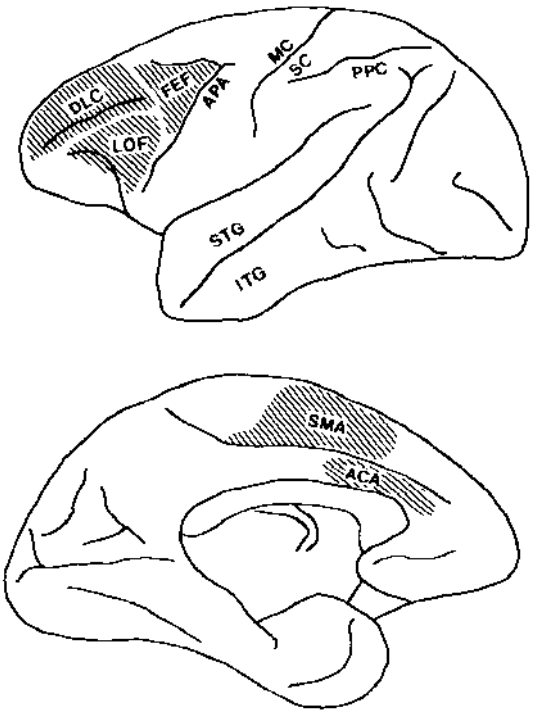

Figure 1 Frontal cortical targets of basal ganglia output. Schematic illustration of the five cortical areas that contribute to the "closed loop" portions of the basal ganglia–thalamocortical circuits discussed in this review.

Abbreviations are as follows: ACA: anterior cingulate area; APA: arcuate premotor area; DLC: dorsolateral prefrontal cortex; FEF: frontal eye fields; ITG: inferior temporal gyrus; LOF: lateral orbitofrontal cortex; MC: motor cortex; PPC: posterior parietal cortex; SC: somatosensory cortex; SMA: supplementary motor area; STG: superior temporal gyrus.

GENERALIZED BASAL GANGLIA–THALAMOCORTICAL CIRCUIT

Sufficient information has now accumulated to support the presentation of a generalized schema that emphasizes the basic features of the proposed basal ganglia–thalamocortical circuits. The elements of each circuit include discrete, essentially non-overlapping parts of the striatum, globus pallidus, substantia nigra, thalamus, and cortex. The basic design of each pathway is thought to be similar, as shown schematically in Figure 2. Each circuit receives multiple, partially overlapping corticostriate inputs, which are progressively integrated in their subsequent passage through pallidum and

nigra to a restricted portion of the thalamus, and from there back to a single cortical area. Each circuit is, therefore, partially closed by the restricted thalamocortical projection returned to one of that circuit's multiple sources of corticostriate input. From the available evidence (discussed below), it would appear that within each of the proposed basal ganglia–thalamocortical circuits the integrative mechanisms that underly the "funneling" of multiple corticostriate inputs back to a single cortical area are progressively carried out at striatal, pallidal/nigral, and thalamic levels. In this limited sense, then, this organizational schema retains the concept of "funneling" that figured so prominently in earlier views. An important distinction, however, is that according to the present view such "funneling"

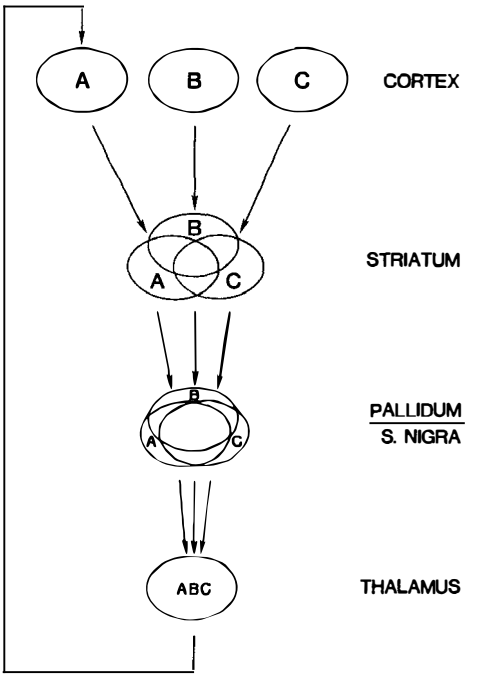

Figure 2 Generalized basal ganglia–thalamocortical circuit. "Skeleton" diagram of the proposed basal ganglia–thelamocortical circuits. Each circuit receives output from several functionally related cortical areas (A, B, C) that send partially overlapping projections to a restricted portion of the striatum. These striatal regions send further converging projections to the globus pallidus and substantia nigra, which in turn project to a specific region of the thalamus. Each thalamic region projects back to one of the cortical areas that feeds into the circuit, thereby completing the "closed loop" portion of the circuit.

occurs only *within* the segregated functional pathways. Moreover, it appears that each basal ganglia–thalamocortical circuit receives its multiple corticostriate inputs only from cortical areas that are functionally related (and usually interconnected). Thus, for example, the "motor" circuit receives inputs from at least four interconnected cortical areas that have been strongly implicated in the control of limb and orofacial movements, while the "oculomotor" circuit receives inputs from three interconnected areas implicated in the control of eye movements.

We emphasize at the outset that our use of the term "circuit" in this review is not intended to imply a rigidly self-enclosed pathway without substantial inputs and outputs to other structures. Rather, the concept we hope to convey is that, despite the influx of diverse influences to each of the basal ganglia–thalamocortical pathways, and the dispersal of influences from these pathways to other structures, there remains a central "closed loop" portion of each basal ganglia–thalamocortical pathway that receives input from and terminates within a single cortical area. It should also be stressed that the proposed linkages between different structures rest for the most part on comparisons of data from independent studies. Where published illustrations of these data have been limited, we have often had to rely on the assumption that different investigators have used the same anatomical terms to refer to the same areas. Also, because of the well-known species differences in the anatomical organization of these nuclei, we have relied primarily on studies in primates. Certain details of the proposed basal ganglia–thalamocortical circuits may eventually require revision. This is especially likely, for example, with respect to the pallido/nigrothalamic connections, where the circuits are maximally compressed and detailed data are most lacking. Future studies, using double labeling and combined anterograde/retrograde techniques in the same animal, are likely to clarify many details that must now be considered provisional.

Because of the parallel nature of the basal ganglia–thalamocortical circuits and the apparent uniformity of synaptic organization at corresponding levels of these functionally segregated pathways (Nauta 1979, DeLong & Georgopoulos 1981), it would seem likely that similar neuronal operations are performed at comparable stages of each of the five proposed circuits. Thus, for example, the neural mechanisms mediating transmission of information through the pallidal portion of the "motor" circuit are likely to be comparable, if not identical, to those within the pallidal portion of the "dorsolateral prefrontal" circuit. If this assumption is correct, then detailed knowledge of the workings of one circuit may prove useful in attempts to clarify another. With this in mind, we shall examine certain physiological data obtained in two of the better understood circuits, the "motor" and oculomotor," in some detail.

"MOTOR" CIRCUIT

At the level of the striatum, the "motor" circuit is largely centered on the putamen, which receives substantial, somatotopically organized projections from the motor (Kunzle 1975) and somatosensory cortices (Kunzle 1977). While the corticostriate projections from the motor cortex overlap with those from the somatosensory cortex, the somatotopic features of both projections are in register. Both motor and somatosensory cortical "leg" areas project to a dorsolateral sector of the putamen, the "face" areas to a ventromedial sector, and the "arm" areas to a region in between (Kunzle 1975, 1977). Each of these terminal fields, like those of other corticostriate projections, is considerably elongated along the rostrocaudal axis. In double anterograde labeling studies, we have found that within the region of gross convergence of corticostriate projections from the "arm" areas of motor and somatosensory cortices, some of the patchy terminal fields from the two areas are in register, while others are not (J. Hedreen, M. R. DeLong, G. E. Alexander, and C. Kitt, unpublished data). Analogous observations have been made with respect to corticostriate projections to the caudate nucleus (Selemon & Goldman-Rakic 1985 (see below).

In addition to the motor and somatosensory projections, the putamen also receives topographically organized projections from area 5, from lateral area 6, including the arcuate premotor area, and from the supplementary motor area (Kunzle 1978, Selemon & Goldman-Rakic 1985, Jones et al 1977, Miyata & Sasaki 1984). While there is slight encroachment of each of these projections upon neighboring regions of the caudate nucleus, the terminal arborizations of each are confined principally to the putamen. It should be noted that published reports of corticostriate projections from the supplementary motor area (Kunzle 1978, Miyata & Sasaki 1984, Selemon & Goldman-Rakic 1985) appear to have been based principally upon injections of anterograde label into the rostrally located "face" representation (see Muakkassa & Strick 1979, Brinkman & Porter 1979), with resultant terminal labeling located mainly within the ventromedial putamen. These results, in combination with those involving injections of anterograde label into more caudal portions ("arm" representation) of the supplementary motor area (A. A. Martino and P. L. Strick, unpublished data), have confirmed the same pattern of somatotopic organization of corticostriate projections observed for motor and somatosensory cortex. It remains to be determined whether there are additional corticostriate inputs to the "motor" circuit from other functionally related regions, such as the precentral and ventral cingulate premotor areas (Muakkassa & Strick 1979), the supplementary somatosensory area, and certain parts of the superior and inferior parietal lobules.

The putamen sends topographically organized projections to the ventrolateral two-thirds of both the internal and the external segments of the globus pallidus (Cowan & Powell 1966, DeVito et al 1980, Johnson & Rosvold 1971, Nauta & Mehler 1966, Parent et al 1984a, Szabo 1962, 1967) and to caudolateral portions of the substantia nigra (Hedreen et al 1980, Nauta & Mehler 1966, Parent et al 1984b, Szabo 1962, 1967). The portion of the internal pallidal segment that receives putamen input projects in turn to the oral part of the ventrolateral nucleus of the thalamus (VLo) (DeVito & Anderson 1982, Kim et al 1976, Kuo & Carpenter 1973, Nauta & Mehler 1966). Recent studies have indicated that the VLo projects to the supplementary motor area (Schell & Strick 1984). Thus, as indicated in Figure 3, somatotopically organized corticostriate influences arising from the supplementary motor area, the arcuate premotor area, motor cortex, and somatosensory cortex are transmitted through the "motor" circuit and ultimately projected back upon a single cortical region, the supplementary motor area. This combination of "open-" and "closed-loop" features appears to be a general characteristic of all basal ganglia-thalamocortical circuits (Figures 2 and 3).

The contribution of the substantia nigra pars reticulata (SNr) to the "motor" circuit has not been fully resolved. Studies of neuronal activity in primates have indicated a prominent representation of orofacial structures in the lateral SNr (DeLong et al 1983b). On the basis of the topographic details revealed in studies reported thus far, it has been suggested (Schell & Strick 1984) that the "face" representation in the lateral SNr may project to the medial subdivision of the ventrolateral nucleus (VLm), but this has yet to be fully established.

A number of lines of evidence indicate that the supplementary motor area, the cortical terminus of the "motor" circuit, plays an important role in the programming and control of movement. The supplementary motor area sends projections not only to the motor cortex and the arcuate premotor area (Muakkassa & Strick 1979, Schell & Strick 1984) but also projects directly to the spinal cord (Biber et al 1978, Murray & Coulter 1981, Macpherson et al 1982, Palmer et al 1981). There is evidence for sparse projections from the supplementary motor area to extreme dorsolateral portions of the ventral horn in lower cervical segments of the spinal cord (G. R. Schell and P. L. Strick, unpublished data). This pattern of termination suggests the existence of direct projections to motor neurons innervating distal hand muscles, and raises the possibility of monosynaptic inputs to spinal motoneurons from the supplementary motor area, analogous to those arising in primary motor cortex. It has been shown that microstimulation of the supplementary motor area in the monkey produces movements of the limbs (Macpherson et al 1982). Neurons in the

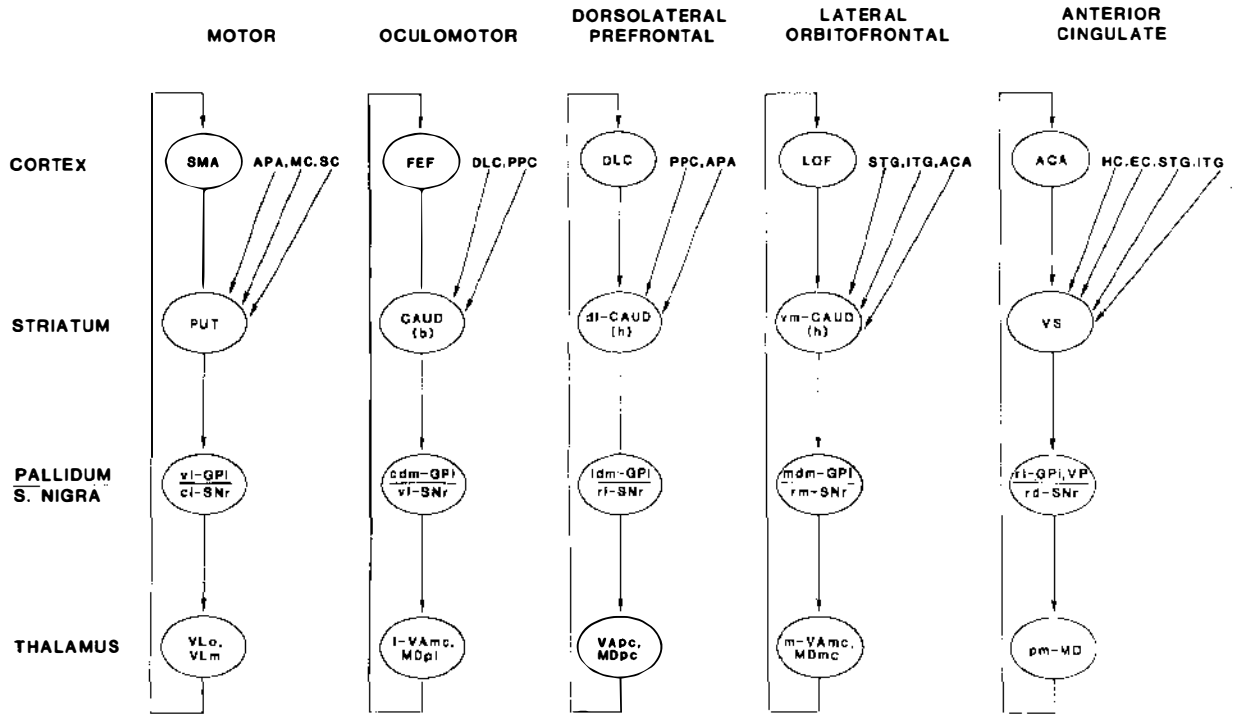

Figure 3 Proposed basal ganglia–thalamocortical circuits. Parallel organization of the five basal ganglia–thalamocortical circuits. Each circuit engages specific regions of the cerebral cortex, striatum, pallidum, substantia nigra, and thalamus.

Abbreviations are as follows: ACA: anterior cingulate area; APA: arcuate premotor area; CAUD: caudate, (b) body (h) head; DLC: dorsolateral prefrontal cortex; EC: entorhinal cortex; FEF: frontal eye fields; GPi: internal segment of globus pallidus; HC: hippocampal cortex; ITG: inferior temporal gyrus; LOF: lateral orbitofrontal cortex; MC: motor cortex; MDpl: medialis dorsalis pars paralamellaris; MDmc: medialis dorsalis pars magnocellularis; MDpc: medialis dorsalis pars parvocellularis; PPC: posterior parietal cortex; PUT: putamen; SC: somatosensory cortex; SMA: supplementary motor area; SNr: substantia nigra pars reticulata; STG: superior temporal gyrus; VAmc: ventralis anterior pars magnocellularis; Vapc: ventralis anterior pars parvocellularis; VLm: ventralis lateralis pars medialis; VLo: ventralis lateralis pars oralis; VP: ventral pallidum; VS: ventral striatum; cl-: caudolateral; cdm-: caudal dorsomedial; dl-: dorsolateral; l-: lateral; ldm-: lateral dorsomedial; m-: medial; mdm-: medial dorsomedial; pm: posteromedial; rd-: rostrodorsal; rl-: rostrolateral; rm-: rostromedial; vm-: ventromedial; vl-: ventrolateral.

supplementary motor area are somatotopically organized, and in single cell studies with behaving primates they have been shown to discharge in relation to limb movements (Brinkman & Porter 1979, Tanji & Kurata 1979) and during the preparation for such movements (Tanji et al 1980).

Two prominent features of the basal ganglia components of the "motor" circuit revealed by single cell recording studies in behaving primates are (*a*) the specificity of neuronal responses to active movements and passive manipulations of individual body parts, and (*b*) the maintained somatotopic organization of movement-related neurons throughout the circuit. The somatotopic organization in the putamen suggested by the topography of the corticostriate projections from motor and somatosensory cortex has been confirmed in studies of the sensorimotor response properties of neurons in awake, behaving primates (Alexander & DeLong 1985a, Crutcher & DeLong 1984, Liles 1979, 1985). Neurons related to active and/or passive movements of the lower extremity are found throughout a long rostrocaudal extent of the dorsolateral putamen; neurons related to orofacial movements are located ventromedially; and neurons related to movements of the upper extremity are located in an intermediate position. Recent studies in monkeys have revealed that movements of individual body parts can be evoked by microstimulation of the putamen (Alexander & DeLong 1985b). Moreover, the microexcitable zones within the putamen (which appear to correspond to clusters of functionally related putamen neurons) are somatotopically organized in precisely the same pattern as that revealed by the distributions of corticostriate terminals and the functional properties of putamen neurons (Alexander & DeLong 1985a). Neurons in both segments of the globus pallidus have also been found to exhibit discrete responses to active movements and passive manipulation of individual body parts (DeLong 1971, DeLong & Georgeopoulos 1979, DeLong et al 1985, Georgopoulos et al 1983) and to be somatotopically organized (DeLong et al 1985).

Neuronal activity in the putamen and globus pallidus has been shown to be related to specific aspects of limb movements, including direction, amplitude (or velocity), and load (Georgopoulos et al 1983, Crutcher & DeLong 1984b, Liles 1985). In the putamen, the directional specificity of movement-related neuronal discharge appears to be relatively independent of patterns of muscular activity (Crutcher & DeLong 1984b). These studies favor a role of the "motor" circuit in the control of movement direction and in the scaling of movement amplitude or velocity. It is noteworthy that in the putamen and globus pallidus the onset of neuronal discharge in relation to stimulus-triggered movements appears to follow that of the cortical motor areas (Crutcher & DeLong 1984b, Georgopoulos et al 1983, DeLong et al 1984). This finding suggests that the basal ganglia receive a "corollary

discharge" or "efference copy" from the cerebral cortex. Although these findings do not support a role of the basal ganglia in the initiation of stimulus-triggered movements, it is suggested that these structures may influence the buildup of muscular activity in the first "agonist burst" and thereby participate in the control of movement speed and amplitude (Hallett & Khoshbin 1980, DeLong et al 1984). It is possible, however, that the "motor" circuit may also play a role in the programming and initiation of internally-generated movements (Evarts & Wise 1984, Neafsy et al 1978).

Recent studies have provided evidence of direct participation of the basal ganglia in the preparation for movement (Alexander 1984). These studies have revealed a population of neurons in the primate putamen that show instruction-dependent changes in discharge related to "motor set" that are similar to those found in motor cortex (Tanji & Evarts 1976), premotor cortex (Weinrich & Wise 1982), and the supplementary motor area (Tanji et al 1980), all of which project to the putamen. It is striking that, in general, set-related cells in the putamen do not show phasic changes during movement or exhibit any response to somatosensory stimulation, suggesting that they may not receive input from phasic movement-related or peripherally-driven neurons of the motor or somatosensory cortex. It remains to be determined whether such set-related influences are integrated at the level of the globus pallidus (and/or thalamus) with the movement- and peripherally-driven influences from the putamen.

Based on the fact that pallidal neurons have large, disk-shaped dendritic arborizations oriented in a plane orthogonal to incoming striatal fibers, it has recently been suggested that the globus pallidus might serve to integrate diverse influences from the striatum, with a resultant loss of specificity and degradation of information content in favor of a more global function (Percheron et al 1984). While theoretically possible on the basis of anatomy alone, this suggestion is not supported by the physiologic evidence indicating maintained specificity of neuronal functional properties within the globus pallidus. Although a single pallidal neuron appears to integrate the output of many putamen neurons, the physiologic findings suggest that at the neuronal level such integration within the "motor" circuit is carried out along lines of individual body parts, without loss of the somatotopic and functional specificity observed in the putamen (De Long et al 1985, Georgopoulos et al 1983).

The evidence for maintained somatotopy and neuronal specificity suggests that the "motor" circuit may be composed of multiple, parallel subcircuits or "channels" concerned with movements of individual body parts. Accordingly, in the generalized circuit depicted in Figure 2, it may be appropriate, depending on the level of analysis, to consider A, B, and C as representing information from somatotopically corresponding subregions

of three separate, but functionally-related cortical areas (e.g. the "arm" representations of the primary motor, somatosensory, and supplementary motor areas). Moreover, within each broad somatotopic area (e.g. the "arm" area) of the putamen, neurons appear to be grouped into multiple functional clusters (with dimensions of 200–1000 μm) that represent a single body part (e.g. the wrist), and often a specific movement of that part (e.g. flexion) (Crutcher & DeLong 1984a, Liles 1979, 1985, Alexander & DeLong 1985a). These observations suggest that the "motor" circuit may be subdivided not only into three broad somatotopic channels representing "leg," "arm," and "face," but perhaps also into functionally-defined channels of an even finer grain, based upon an individual body part or even a specific movement of an individual body part. It remains to be determined whether the functional subunits (neuronal clusters) of the putamen project selectively to comparable subunits in the pallidum (and similarly for the pallidothalamic and thalamocortical projections). The answer to this question would help to clarify the "fine structure" and the nature of integration within the somatotopic channels of the "motor" circuit. Such information may prove helpful in analyzing the nature of information processing within the other basal ganglia–thalamocortical circuits.

The discontinuous distribution of putamen neuronal clusters and microexcitable zones suggests comparisons with certain anatomical and histochemical discontinuities recently identified in the neostriatum. Autoradiographic studies in the monkey have shown that projections to the putamen from the sensorimotor cortex (Jones et al 1977, Kunzle 1975) and from the centromedian nucleus of the thalamus (Kalil 1978) terminate in discontinuous patches and stripes. Moreover, histochemical, histofluorescence, and immunocytochemical studies have revealed similar discontinuities in the distributions of markers for the following putative neurotransmitters and neuromodulators: acetylcholine (Graybiel & Ragsdale 1978, Graybiel et al 1981), dopamine (Grabiel et al 1981), enkephalin (Graybiel et al 1981, Pickel et al 1980) and other opiates (Herkenham & Pert 1981), and substance P (Graybiel et al 1981). It has been suggested that the heterogeneous distribution of anatomical and biochemical markers may reflect an underlying cytoarchitectural organization of the neostriatum in terms of what Graybiel et al (1981) have called "striosomes" and what Goldman-Rakic (1982) has referred to as the "island" and "matrix" compartments. The dimensions of these compartments are remarkably similar to the dimensions of the clusters of functionally related putamen neurons and those of the striatal microexcitable zones (Alexander & DeLong 1985a,b, Crutcher & DeLong 1984a, Goldman-Rakic 1982, Liles 1979).

In both cats and monkeys, corticostriate fibers arising in the frontal

cortex have been shown to terminate largely within the compartment that stains strongly for acetylcholinesterase (Ragsdale & Graybiel 1981). Furthermore, injections of horseradish peroxidase into pallidum and substantia nigra in cats have revealed preferential labeling of presumptive striatal projection neurons in acetylcholinesterase-rich zone (Graybiel et al 1979). Thus, these results suggest that the corticostriate terminal patches, the clusters of retrogradely labeled striatal projection neurons, and the zones of high acetylcholinesterase activity may occupy the same anatomic compartment. However, the degree to which corticostriate afferents may terminate selectively upon clusters of striatal projection neurons remains unknown. Nor is it known to what extent these anatomical findings, based primarily on studies of the caudate nucleus, are applicable to the putamen. Additional studies will be needed to clarify the relationships that may exist between the newly described physiological subunits and the various histochemical compartments of the primate neostriatum.

"OCULOMOTOR" CIRCUIT

The frontal eye fields (Brodmann's area 8) have been shown to project to a central portion of the body of the caudate nucleus (Kunzle & Akert 1977) that also receives projections from dorsolateral prefrontal cortex (areas 9 and 10) and posterior parietal cortex (area 7) (Yeterian & VanHoesen 1978, Selemon & Goldman-Rakic 1985). Each of these interconnected cortical areas has been implicated in oculomotor control mechanisms on the basis of single-cell recording studies in awake monkeys (Bizzi & Schiller 1970, Goldberg & Bushnell 1981, Lynch et al 1977), and the demonstration of direct projections to the superior colliculus (Fries 1984, Leichnetz et al 1981, Goldman & Nauta 1976, Kunzle et al 1976).

The body of the caudate projects to a caudal and dorsomedial sector of the internal pallidal segment and to the ventrolateral SNr (Parent et al 1984a, Szabo 1970). The latter projects in turn to parts of the magnocellular portion of the ventral anterior (VAmc) and the paralamellar portion of the mediodorsal (MDpl) thalamic nuclei (Carpenter et al 1976, Ilinsky et al 1985). Both of these thalamic areas project back to the frontal eye fields (Kievit & Kuypers 1977, Akert 1964, Barbas & Mesulam 1981), as indicated in Figure 3, thus partially closing the "oculomotor" circuit. There are indications that at least part of the nigrothalamic projection may represent branching collaterals from SNr neurons that also project to the superior colliculus (Anderson & Yoshida 1977, Parent et al 1984b, Beckstead et al 1981), suggesting that the nigrotectal pathway may provide an important direct output pathway for the "oculomotor" circuit.

Single cell studies in primates have revealed that frontal eye field neurons

may discharge in relation to visual fixation, saccadic eye movements, or passive visual stimulation (Mohler et al 1973, Bizzi & Schiller 1970). The visual receptive field properties of some frontal eye field neurons have been shown to depend upon the animal's behavioral set, in that the cell's response to a visual stimulus within its receptive field may be enhanced when that stimulus serves as the target for a subsequent saccade (Goldberg & Bushnell 1981). Comparable studies of caudate neurons have yet to be reported. However, the ventrolateral SNr, which appears to receive the frontal eye field influences via projections from the body of the caudate, contains neurons that discharge selectively in relation to passive visual stimulation, fixation of gaze, and both visually-triggered and memory-contingent saccadic eye movements (Hikosaka & Wurtz 1983a–c). There is strong evidence that these neurons may participate in the control of saccadic eye movements via a GABAergic nigrotectal projection to the superior colliculus (Hikosaka & Wurtz 1983d, 1985a,b).

As noted above, the lateral SNr also receives projections from portions of the putamen involved in the "motor" circuit (Parent et al 1984a, Szabo 1967), but fibers from the putamen terminate more dorsally than do those from the body of the caudate (Szabo 1970). That these two fiber systems are merely closely juxtaposed rather than convergent is further suggested by the fact that neurons in the lateral SNr appear to discharge selectively either in relation to eye movements or to orofacial movements, but not both (DeLong et al 1983a,b, Hikosaka & Wurtz 1983a–c).

"DORSOLATERAL PREFRONTAL" CIRCUIT

It had been proposed previously that a single "complex" or "association" loop passed through the caudate nucleus and eventually influenced certain prefrontal "association" areas (DeLong & Georgopoulos 1981, DeLong et al 1983b). Subsequent anatomical findings have prompted a reappraisal of this scheme, and it now appears that there are at least two distinct basal ganglia–thalamocortical circuits that selectively influence separate prefrontal areas. Although there is considerable evidence indicating significant functional differentiation between these regions, the behavioral functions associated with each of the proposed "prefrontal" circuits have not yet been characterized to the same degree as have those of the "motor" and "oculomotor" circuits. Accordingly, we have chosen for the time being to give anatomical rather than functional designations to the two "prefrontal" circuits. We discuss each separately in this and the following sections.

The cortex within and around the principal sulcus and on the dorsal prefrontal convexity (Brodmann's areas 9, 10; Walker's area 46) provides the "closed loop" portion of the corticostriate input to the "dorsolateral

prefrontal" circuit (see Figure 1). The projection from this cortical area terminates within the dorsolateral head of the caudate nucleus and throughout a continuous rostrocaudal expanse that extends to the tail of the caudate (Goldman & Nauta 1977, Selemon & Goldman-Rakic 1985, Yeterian & VanHoesen 1978). Grossly overlapping corticostriate projections to this same sector arise from the posterior parietal cortex (area 7) and the arcuate premotor area (Kunzle 1978, Miyata & Sasaki 1984, Selemon & Goldman-Rakic 1985).

Early anterograde transport studies were interpreted as indicating partial convergence of corticostriate projections from interconnected cortical association areas (Yeterian & VanHoesen 1978). Recently, it has been shown by means of double-label anterograde transport that although interconnected areas may project to the same general region in the neostriatum, the terminal arborizations of such projections frequently interdigitate rather than overlap (Selemon & Goldman-Rikac 1985). This finding suggests that the degree of maintained segregation within the basal ganglia–thalamocortical circuits, at least at the level of the striatum, may in fact be more pronounced than is evident from conventional single-label anatomical studies, which rely on comparisons of anterograde and/or retrograde labeling patterns across animals.

Rostral portions of the caudate nucleus project to the dorsomedial one-third of the globus pallidus and to rostral portions of the SNr (Szabo 1962, Johnson & Rosvold 1971, Cowan & Powell 1966, Parent et al 1984a). Within each of these projections there is a mediolateral gradient such that projections from the dorsolateral caudate (which is the recipient of projections from dorsolateral prefrontal cortex) are distributed to more lateral portions of the pallidum and nigra than are those from the ventromedial caudate. The dorsomedial one-third of the internal pallidal segment has been shown to project to the parvocellular portion of the ventral anterior thalamic nucleus (VApc) (Kuo & Carpenter 1973, Kim et al 1976). The VApc projects to regions on the convexity of the frontal lobe, including caudal prefrontal areas (Kievit & Kuypers 1977). The rostrolateral portions of the SNr have been shown to project to the MDpc (Ilinsky et al 1985), which in turn projects to dorsolateral prefrontal cortex in and around the principal sulcus (Akert 1964, Jacobson et al 1978, Pribram et al 1953). Thus, as indicated in Figure 3, the "dorsolateral prefrontal" circuit is partially closed by thalamocortical projections from both the VApc and MDpc.

The "dorsolateral prefrontal" circuit has not been functionally characterized to the same extent as have the "motor" or "oculomotor" circuits, but there are indications from lesioning and single cell recording studies that

this system may participate in processes subserving spatial memory (Alexander et al 1980, Fuster & Alexander 1973, Fuster 1981, Goldman et al 1971, Isseroff et al 1982, Divac et al 1967).

"LATERAL ORBITOFRONTAL" CIRCUIT

Lateral orbitofrontal cortex (Brodmann's area 10, Walker's area 12) projects to a ventromedial sector of the caudate nucleus that extends from the head to the tail of this structure. This part of the caudate also receives input from the auditory and visual association areas of the superior and inferior temporal gyri, respectively (Selemon & Goldman-Rakic 1985, VanHoesen et al 1981, Yeterian & VanHoesen 1978).

Ventromedial portions of the caudate project to a dorsomedial sector of the internal pallidal segment that lies just medial to the sector innervated by the dorsolateral caudate, and to a rostromedial portion of the SNr (Johnson & Rosvold 1971, Szabo 1962). The latter projects in turn to medial parts of the VAmc and to the MDmc (Carpenter et al 1976, Ilinsky et al 1985). The "closed loop" portion of the "lateral orbitofrontal" circuit is thus completed by return projections from these two thalamic regions to the lateral orbitofrontal cortex (see Figure 1) (Ilinsky et al 1985), as indicated in Figure 3.

Like the other "prefrontal" basal ganglia loop, the "lateral orbitofrontal" circuit has yet to be fully characterized from a functional standpoint. It has been shown that bilateral lesions in primates restricted either to the lateral orbitofrontal area or to the portion of the caudate to which it projects appear to result in a perseverative interference with an animal's capacity to make appropriate switches in behavioral set (Divac et al 1967, Mishkin & Manning 1978). It remains to be seen whether lesions placed selectively at other points in this circuit will produce the same disruptions of behavior. With respect to possible future investigations of this pathway at the single cell level, it is likely that considerable ingenuity will be required to devise suitable behavioral paradigms for the functional characterization of the constituent neurons.

"ANTERIOR CINGULATE" CIRCUIT

Barely a decade has passed since the concept of the ventral striopallidal system was first proposed (Heimer & Wilson 1975). The concept was based upon striking parallels, in a number of species, between the connections and histochemical features of the neostriatum and those of the nucleus accumbens and the medium-celled portion of the olfactory tubercle

(Heimer & Wilson 1975, Heimer 1978, Heimer et al 1977, Nauta 1979). Because both subdivisions of the ventral striatum (accumbens and olfactory tubercle) receive extensive projections from so-called "limbic" structures, including the hippocampus, the amygdala, and entorhinal (area 28) and perirhinal cortices (area 35) (Heimer & Wilson 1975, Hemphill et al 1981, Kelley & Domesick 1982, Kelley et al 1982, Krayniak et al 1981, Nauta 1961), this portion of the striatum has been referred to as the "limbic" striatum (Nauta & Domesick 1984). Although the ventral striatum was once believed to receive its cortical input exclusively from nonisocortical areas, recent evidence indicates that there are also significant projections to this region from the anterior cingulate area (area 24) and widespread sources in the temporal lobe, including the temporal pole and the superior and inferior temporal gyri (Baleydier & Mauguiere 1980, Hemphill et al 1981, Powell & Leman 1976, Selemon & Goldman-Rakic 1985, VanHoesen et al 1976, 1981, Yeterian & VanHoesen 1978). There are indications that the accumbens may also receive projections from posterior portions of the medial orbitofrontal area (area 11 of Brodmann, Walker's area 13, area FF of Bonin & Bailey) (Nauta 1962, Yeterian & Van Hoesen 1978).

The ventral striatum has been shown in rats to project to the precommissural or ventral pallidum and to the substantia nigra (Heimer 1978, Nauta et al 1978). Recent anterograde transport studies have revealed that in the monkey the nucleus accumbens projects not only to the ventral pallidum and rostrodorsal substantia nigra, but also to a rostrolateral sector of the internal pallidal segment (J. Hedreen and M. R. DeLong, unpublished data), which projects in turn to a paramedian portion of the MDmc (Kuo & Carpenter 1973). The "anterior cingulate" circuit thus appears to be partially closed by the well-documented projections to the anterior cingulate area from posterior and medial portions of the mediodorsal nucleus (MD) (Baleydier & Mauguiere 1980, Jurgens 1983, Tobias 1975, Vogt et al 1979), as indicated in Figure 3.

The functional characteristics of this circuit cannot as yet be specified in any detail. The hippocampal and enterhinal inputs to this pathway are generally considered to be "limbic" structures, and by virtue of their connectivity and lamination (which is intermediate between that of isocortex and that of allocortex), several of the neocortical inputs (anterior cingulate, medial orbitofrontal, and temporal pole) have been designated as "paralimbic association" cortex (Pandya & Seltzer 1982). Considering the uncertainties surrounding the functions of the so-called "limbic" structures, and the paucity of behavioral and physiological data in the primate, it is difficult even to speculate on the possible functions that may be subserved by the "anterior cingulate" circuit. It is for this reason that we have employed a purely anatomical term to designate this proposed circuit.

SUBSIDIARY BASAL GANGLIA CIRCUITS

In addition to the five principal circuits outlined above, the individual nuclei of the basal ganglia also participate in several subsidiary circuits, which apparently serve, at least in part, to modify transmission through the basal ganglia–thalamocortical pathways. The nodal points of these subsidiary circuits include the subthalamic nucleus (Nauta & Cole 1978), the intralaminar nuclei of the thalamus (Kalil 1978, Parent et al 1983), the pedunculopontine nucleus (Parent et al 1983), and the dopaminergic nuclei of the mesencephalic tegmentum (Carpenter & Peter 1972, Parent et al 1983). It is beyond the scope of this review to consider these circuits in any detail. It should be noted, however, that the topographic features characteristic of the principal circuits are also found in these subsidiary circuits. Moreover, both the centromedian nucleus (Kunzle 1976) and the subthalamic nucleus (Monakow et al 1978) appear to be somatotopically organized by virtue of topographically organized projections from the motor cortex.

In addition to input from the cortex and thalamus, the striatum also receives projections from the nuclei of the dorsal raphe (DeVito et al 1980, Parent et al 1983), the locus coeruleus (Parent et al 1983), and the amygdala (Nauta 1961, Parent et al 1983, Russchen et al 1985). Presumably, these inputs also serve to modify the transfer of information through the various basal ganglia–thalamocortical circuits.

BEHAVIORAL AND CLINICAL IMPLICATIONS

We hope that the conceptual framework of segregated functional circuits that we have proposed may prove useful not only in attempts to clarify the normal functions of the basal ganglia, but also in efforts to understand the behavioral and motor disturbances that occur in disorders involving the basal ganglia, such as Parkinson's and Huntington's diseases. To the extent that this framework is an accurate representation of the structural and functional organization of the basal ganglia in normal individuals, it may prove useful in suggesting pathophysiologic mechanisms to account for some of the clinical manifestations of these disorders.

Several features of the proposed scheme of basal ganglia organization are of obvious relevance to the understanding of the symptoms of basal ganglia disorders. At the most basic level, the separation of the "motor" and "prefrontal" circuits provides a framework whereby relatively selective disturbances of "motor" or more "complex" behavior may occur from damage to different portions of the basal ganglia. As discussed above, there is considerable evidence for such dissociations in experimental studies in

primates (DeLong & Georgopoulos 1981, Divac et al 1967). Furthermore, the existence of channels for the control of individual body parts in the "motor" circuit helps to clarify how involuntary movements or impairments of movements of a single body part (e.g. monochorea, focal dystonias, or focal dyskinesias) may result from restricted lesions or disturbances within these nuclei.

The finding that the supplementary motor area receives the output from the "motor" circuit provides a new perspective on the motor functions of the basal ganglia. Considerable evidence now exists for a role of the supplementary motor area in the programming, initiation, and execution of movement. For example, recent studies in humans indicate increased cerebral blood flow (and therefore increased metabolic activity) in the region of the supplementary motor area (but not in other regions) during the planning or rehearsal of complex movement sequences. Moreover, the supplementary motor area has been found to be active during the execution of complex but not simple finger movements (Roland et al 1980); this finding may reflect the relative requirements for programming in the two tasks. Additional evidence for a role of the supplementary motor area in the programming of movement comes from single cell studies in monkeys, which have revealed changes in neuronal activity during periods when the animal is preparing to make a movement (Tanji et al 1980). This activity appears to reflect the "motor set" of the animal. Thus, it would appear that the basal ganglia and the supplementary motor area form part of a system involved in the programming and execution of complex movements. It has been suggested that some of the motor abnormalities seen in Parkinson's disease might be understood in terms of the relations between the basal ganglia and the supplementary motor area (Schell & Strick 1984). In view of the supplementary motor area's apparent role in motor programming, it is of interest that patients with Parkinson's disease often show impairments in predictive tracking movements (Flowers 1978) and other complex aspects of movement that require motor programming (Marsden 1984). It is noteworthy that certain motor disturbances characteristic of Parkinson's disease have occasionally been observed in patients with lesions that involve the supplementary motor area. There are reports of global akinesia, maximal contralaterally, associated with lesions of the supplementary motor area in man (Damasio & VanHoesen 1980, LaPlane et al 1977). As one of the cardinal signs of Parkinson's disease, akinesia is generally attributed to the loss of dopaminergic input to the striatum that results from degeneration of the pars compacta of the substantia nigra. Thus, it is conceivable that the disruption of striatal dopaminergic transmission that occurs in patients with Parkinson's disease might result in akinesia as a consequence of disordered basal ganglia inputs to the supplementary

motor area. This suggestion, however, is difficult to reconcile with the paucity of motor deficits observed in monkeys with lesions of the supplementary motor area (Brinkman 1984, Travis 1955), in whom the most consistent finding appears to be a moderate disruption of coordinated bimanual movements. It remains to be determined whether these discrepancies between human and simian studies represent true species differences, or are related instead to possible differences in the precise locations of the damaged areas.

The importance of the "oculomotor" circuit in the control of eye movements has been brought into clearer focus by recent anatomical and physiological studies. Among other major clinical manifestations, patients with Huntington's disease—in whom there is profound degeneration of the caudate nucleus (and to a lesser extent the putamen)—often show severe disturbances in the initiation of voluntary saccades, and their saccades may be markedly slowed (Leigh et al 1983). These observations might be explained by an increase in the tonic, GABAergic nigrocollicular discharge (Hikosaka & Wurtz 1985b), which would be expected if degeneration of the "oculomotor" portion of the caudate nucleus resulted in decreased phasic disinhibition along the caudate-SNr-thalamic/collicular pathway.

While it is generally accepted that disturbances of motor function may result from basal ganglia damage, the precise role of the basal ganglia in disturbances of higher functions in humans is still controversial because of the often associated neuropathologic changes occurring in other structures. The cognitive deficits in patients with Huntington's disease, for example, might be accounted for, at least partially, by degeneration of the caudate nucleus with consequent interruption of the "dorsolateral prefrontal" or "lateral orbitofrontal" circuits. This suggestion would be difficult to prove, however, in view of the widespread cortical degeneration that is a frequent accompaniment of Huntington's disease. Nevertheless, it is noteworthy that recent positron emission tomographic studies have revealed that dementia in Huntington's disease is correlated with hypometabolism in the caudate nucleus rather than in the cerebral cortex (Kuhl et al 1982).

CONCLUDING REMARKS

Although the basal ganglia lack gross cytoarchitechtonic differentiation and were long viewed as lacking in specificity of connection and function, the anatomic and physiologic evidence accumulated over the past two decades has revealed a level of organization and functional specificity paralleling that of the cerebral cortex itself. We have reviewed the evidence relevant to our proposal that the basal ganglia be viewed as components of multiple parallel, segregated circuits. Each of the five proposed basal

ganglia–thalamocortical circuits appears to receive input from several separate but functionally related cortical areas, traverse specific portions of the basal ganglia and thalamus, and project back upon one of the cortical areas providing input to the circuit, thus forming a partially "closed" loop (Figure 2).

Although we have placed emphasis on the segregation of functional circuits, this should not be construed as implying that integration is a minor function of these pathways. We have attempted to show that integration within each circuit appears to be of a highly specific nature, as exemplified by the retention of detailed place and modality specificity within the "motor" circuit despite progressive convergence of separate cortical influences along the pathways leading to the ventrolateral thalamus.

Multiple subsidiary circuits appear to modify and modulate the flow of information through the major basal ganglia–thalamocortical pathways and to provide additional routes for influences to be exerted on other structures. It is obvious that the basal ganglia should no longer be viewed as "centers" or structures having a role independent of the cerebral cortex and thalamus, with which they have intimate and highly specific afferent and efferent connections. Accordingly, from the functional standpoint it would seem more appropriate to attempt an appraisal of the distinctive functions of the individual basal ganglia–thalamocortical circuits than to try to assign functions to their component nuclei. Furthermore, in view of the apparently uniform organization of the five principal circuits, it would seem that the operations performed at the same levels of each circuit are likely to be quite comparable, even though the information transmitted through the individual circuits might differ considerably. It is possible, therefore, that knowledge about the operations performed at a particular level of one circuit, e.g. the pallidal portion of the "motor" circuit, might also be applicable to those performed at the same level of the other basal ganglia–thalamocortical circuits.

Future research may reveal functional subdivisions of the "oculomotor," "prefrontal," and "anterior cingulate" circuits comparable to the somatotopic channels within the "motor" circuit. For example, the "oculomotor" circuit might contain separate, parallel channels arranged according to a retinocentric (or, on the other hand, a spatial) coordinate system. For the present, the nature of the channels that might exist in the "prefrontal" and "anterior cingulate" circuits remains a matter for speculation, pending further clarification of the functional roles of these pathways. That there may be additional basal ganglia–thalamocortical circuits, beyond those proposed here, seems likely. This question can only be answered, however, by further anatomical and functional studies. Considering the enormous expansion of the frontal lobes in man and the selective targeting of basal

ganglia influences on these frontal areas, it is even possible that circuits exist in man for which there are no counterparts in the monkey.

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