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A Revised Neuroanatomy of Frontal–Subcortical Circuits

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A major feature of basal ganglia anatomy is their participation in multiple loops with the cerebral cortex. One way to characterize the structure of these circuits is to divide them into sets of "input" and "output" nuclei. The input nuclei consist of the caudate, putamen, and ventral striatum. All of these regions receive direct projections from the cerebral cortex (reviewed in Alexander, DeLong, & Strick, 1986; Parent & Hazrati, 1995). The major output nuclei consist of the internal segment of the globus pallidus (GPi) and the pars reticulata of the substantia nigra (SNr). Both of these nuclei send efferents to thalamic nuclei that project back upon the cerebral cortex. Other nuclei within the basal ganglia receive some direct input from the cerebral cortex (e.g., the subthalamic nucleus [STN]) or send some efferents to the thalamus (e.g., the projection from the external segment of the globus pallidus [GPe] to the reticular nucleus). However, GPe and STN, along with the pars compacta of the substantia nigra (SNc), are generally thought to represent "intermediate" stages of processing that modulate activity in basal ganglia circuits (see Carlsson & Carlsson, 1990; Parent & Hazrati, 1995).

An important issue concerning the organization of basal ganglia loops with the cerebral cortex has been the degree of anatomical convergence or segregation that takes place between them. The traditional view was that these loops collect information from widespread cortical areas. These signals were then thought to be "funneled" through a series of anatomical connections, until their ultimate convergence at the level of basal ganglia output nuclei. Efferents from the output nuclei were thought to innervate

subdivisions of the ventrolateral thalamus projecting exclusively upon the primary motor cortex (M1) or the supplementary motor area (SMA) (see, e.g., Kemp & Powell, 1971). Thus, basal ganglia loops were thought to function solely in the domain of motor control.

It is now clear that the inputs to the basal ganglia from a variety of cortical areas remain largely segregated throughout the successive stages of basal ganglia processing (reviewed in Alexander et al., 1986; Parent & Hazrati, 1995; Strick, Dum, & Picard, 1995). Moreover, basal ganglia efferents innervate a diverse group of thalamic nuclei that have projections to regions of the cerebral cortex beyond M1 and the SMA, including areas of prefrontal cortex, and even areas outside the frontal lobe (reviewed in Alexander et al., 1986; see also Barbas, Haswell Henion, & Dermon, 1991; Dermon & Barbas, 1994; Goldman-Rakic & Porrino, 1985; Middleton & Strick, 1996, 2000). In this chapter, we summarize results from some of our recent experiments that have examined the organization of basal ganglia loops with the cerebral cortex. These and other results have led us to propose that the output of the basal ganglia influences the function of a remarkably diverse set of cortical areas. Furthermore, our observations have led us to propose that multiple closed loops characterize the major form of interaction between the basal ganglia and cerebral cortex.

HISTORICAL PERSPECTIVE

Alexander and colleagues (1986) proposed that the basal ganglia participate in five parallel segregated circuits with selected cortical areas in the frontal lobe. Two of these circuits were thought to be related to motor function and to influence skeletomotor and oculomotor areas of cortex. The remaining three loops were with nonmotor areas in the frontal lobe, including the dorsolateral prefrontal cortex, the lateral orbitofrontal cortex, and the anterior cingulate/medial orbitofrontal cortices. These frontal regions are known to be involved in aspects of planning, working memory, rule-based learning, attention, and emotional regulation (for reviews, see Fuster, 1997; Goldman-Rakic, 1987). Thus, according to Alexander and colleagues, the basal ganglia are able to influence a broad range of motor and nonmotor behavior.

Efforts to evaluate the circuitry proposed by Alexander and colleagues (1986) were faced with a number of technical limitations. Chief among these was the inability of most conventional anatomical techniques to trace multisynaptic connections in the brain. In recent years, this limitation has been overcome with the development of techniques for using neurotropic viruses as transneuronal tracers. This technique enables investigators to identify second- and in some instances third-order neurons in the basal ganglia that either receive input from or project to a specific area of cerebral

cortex (Hoover & Strick, 1999; Strick & Card, 1992; Zemanick, Strick, & Dix, 1991). We have extensively used this viral tracing technique to examine the structure of basal ganglia–thalamocortical pathways in monkeys (Hoover & Strick, 1993, 1999; Lynch, Hoover, & Strick, 1994; Middleton & Strick, 1994, 1996). Based largely on these studies, and also a number of others that have used double labeling with conventional tracers (Ilinsky, Jouandet, & Goldman-Rakic, 1985; Inase & Tanji, 1995; Percheron, Francois, Talbi, Yelnik, & Fenelon, 1996; Rouiller, Liang, Babalian, Moret, & Wiesendanger, 1994; Sakai, Inase, & Tanji, 1996), we suggest two key modifications to the scheme proposed by Alexander and colleagues.

The first modification involves the number of cortical areas that are the targets of basal ganglia output. Many of the cortical regions that were thought to be merely sources of afferents to the input stage of basal ganglia processing are now known to be the targets of efferents from the output stage of basal ganglia processing. Current evidence suggests that each of the circuits previously described by Alexander and colleagues (1986) is in fact composed of multiple subcircuits.

The second modification concerns the variety of cortical areas influenced by basal ganglia output. There is growing evidence that the output of the basal ganglia extends beyond the frontal lobe to influence areas of cortex as diverse as inferotemporal cortex and possibly posterior parietal cortex (see Middleton & Strick, 1996). All told, we believe that current evidence supports the existence of multiple basal ganglia loops with the cerebral cortex. These can be grouped into seven general categories: skeletomotor, oculomotor, dorsolateral prefrontal, lateral orbitofrontal, medial orbitofrontal, anterior cingulate, and inferotemporal/posterior parietal. The circuits in each of these categories are discussed in separate sections below.

SKELETOMOTOR LOOPS

The skeletomotor circuit (Figure 2.1A) originally proposed by Alexander and colleagues (1986) was thought to collect information from multiple motor and premotor areas of cortex (e.g., M1 and the "arcuate premotor area" [now called the ventral premotor area or PMv], as well as the SMA). The signals from these different cortical areas were thought to be received by the putamen and sent via GPi and the ventrolateral thalamus (the nucleus ventralis anterior [VA] and nucleus ventralis lateralis [VL]) back to the cerebral cortex. However, this output was only believed to project back upon the SMA. Since their proposal, multiple regions of M1 (the face, arm, and leg representations), as well as the arm representations of the SMA and PMv, have all been shown to be the targets of output from GPi (Hoover & Strick, 1993, 1999; Strick, Hoover, & Mushiake, 1993; Zemanick et al., 1991). Moreover,
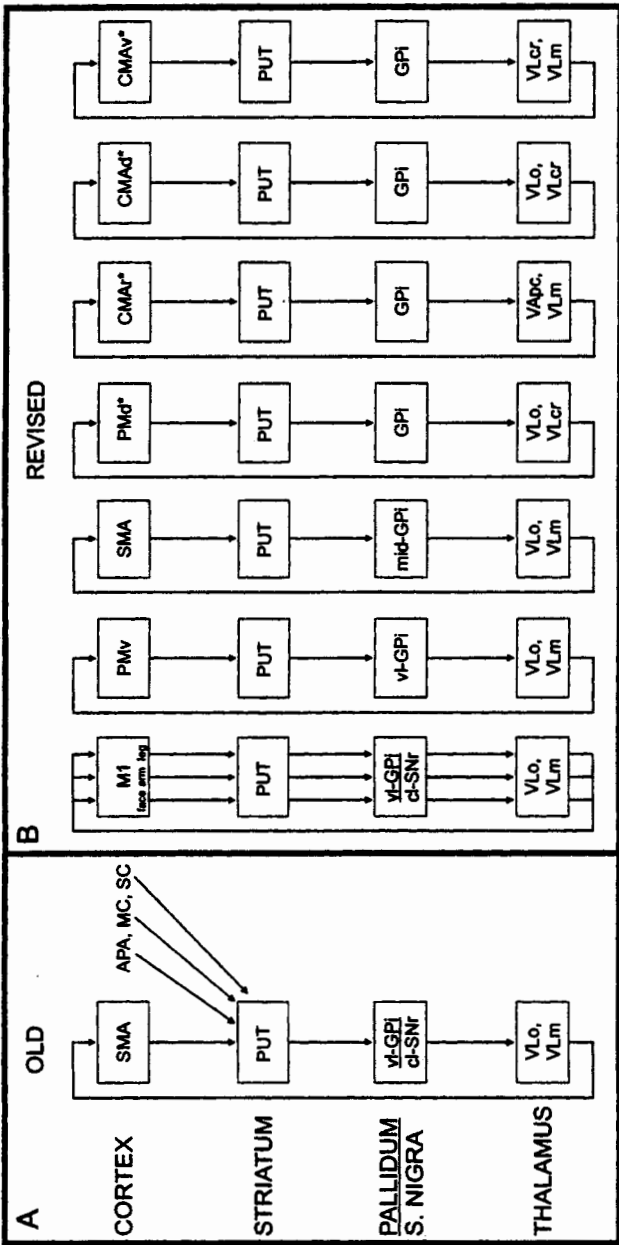
FIGURE 2.1. The original motor circuit proposed by Alexander, DeLong, and Strick (1986) and our revised scheme (A and B, respectively). Asterisks indicate loops whose existence is not yet proven. Cortical abbreviations: APA, arcuate premotor area; CMAd, dorsal cingulate motor area; CMAr, rostral cingulate motor area; CMAv, ventral cingulate motor area; MC/M1, primary motor cortex; PMd, dorsal premotor area; PMv, ventral premotor area; SMA, supplementary motor area. Basal ganglia abbreviations: GPi, internal segment of globus pallidus; PUT, putamen; SNr, substantia nigra pars reticulata; cl, caudolateral; mid, middle; vl, ventrolateral. Thalamic abbreviations (according to Olszewski, 1952): VApc, nucleus ventralis anterior, parvocellular portion; VLcr, nucleus ventralis lateralis pars caudalis, rostral division; VLm, nucleus ventralis lateralis pars medialis; VLo, nucleus ventralis lateralis pars oralis.

the pallidal projection to each cortical area originates from a topographically distinct region of the nucleus that we have termed an "output channel" (Hoover & Strick, 1993; Strick et al., 1993). Largely separate output channels innervate different cortical areas. Specifically, M1 receives input from GPi neurons located in midventral regions of the nucleus. The output channel innervating the arm area of the SMA is located more dorsally, whereas the output channel to the arm area of the PMv is located more ventrally. Within the M1 output channel, neurons influencing the leg, arm, and face areas of M1 are somatotopically organized in a dorsal-to-ventral fashion. Part of the output channel that projects to the face area of M1 is located in a dorsal portion of SNr (Hoover & Strick, 1999).

The presence of distinct output channels and the pattern of inputs to them provide some insight into the nature of processing within individual basal ganglia loops with the cerebral cortex (see Alexander et al., 1986). The M1, SMA, and PMv are all known to project in a highly topographic fashion to the putamen (reviewed in Alexander et al., 1986; Strick et al., 1995). The projections from the putamen to GPi are also topographically organized. These input–output patterns suggest that each of these cortical motor areas is part of a closed-loop circuit with the basal ganglia. Thus the major source of cortical input to a specific circuit appears to be the major target of output from the circuit.

To date, we have examined only a small number of the cortical motor areas that may be involved in basal ganglia processing. In addition to the SMA and PMv, there are four other premotor areas in the frontal lobe that project directly to both M1 and the spinal cord (Dum & Strick, 1991). These and several other related areas of cortex are known to have projections to the input stage of basal ganglia processing. They are also likely to be the targets of basal ganglia output, based on the pattern of thalamic input each receives. For example, the dorsal premotor area (PMd) receives thalamic input from portions of VLo and rostral VLc (Tian & Lynch, 1997). Both of these thalamic areas are known to be the targets of efferents from GPi. A premotor area located caudally on the dorsal bank of the cingulate sulcus (CMAd) also receives >60% of its total thalamic input from VLo and other areas of ventrolateral thalamus that are the targets of efferents from GPi (Holsapple & Strick, 1989). In fact, there is evidence that each of the premotor areas in the frontal lobe may be the target of at least some output from the basal ganglia. Since each of the premotor areas also projects into the input stage of basal ganglia processing, the skeletomotor circuit may actually consist of seven or more distinct loops (Figure 2.1B).

OCULOMOTOR LOOPS

The initial hypothesis of Alexander and colleagues (1986) stated that oculomotor function is subserved by a single loop. The frontal eye field

(FEF) in area 8, along with several related cortical areas, was thought to form the major input to this circuit. The remainder of the loop was believed to involve portions of the caudate, caudal dorsomedial GPi/ventrolateral SNr, and thalamic neurons in lateral VAmc/paralaminar MD (Figure 2.2A). The existence of an output channel in SNr directed toward a region in the FEF that is concerned with the control of saccadic eye movements has been confirmed using virus tracing (Lynch et al., 1994). Recent anatomical experiments with conventional tracers suggest that additional oculomotor loops exist (Tian & Lynch, 1997). For example, the region of the FEF that is concerned with the control of smooth pursuit eye movements receives a major portion of its input from thalamic regions that are the targets of efferents from GPi. Similarly, the supplementary eye field (SEF), located near the medial wall of the hemisphere, also receives a significant input from thalamic regions where pallidal efferents terminate. Thus it is possible
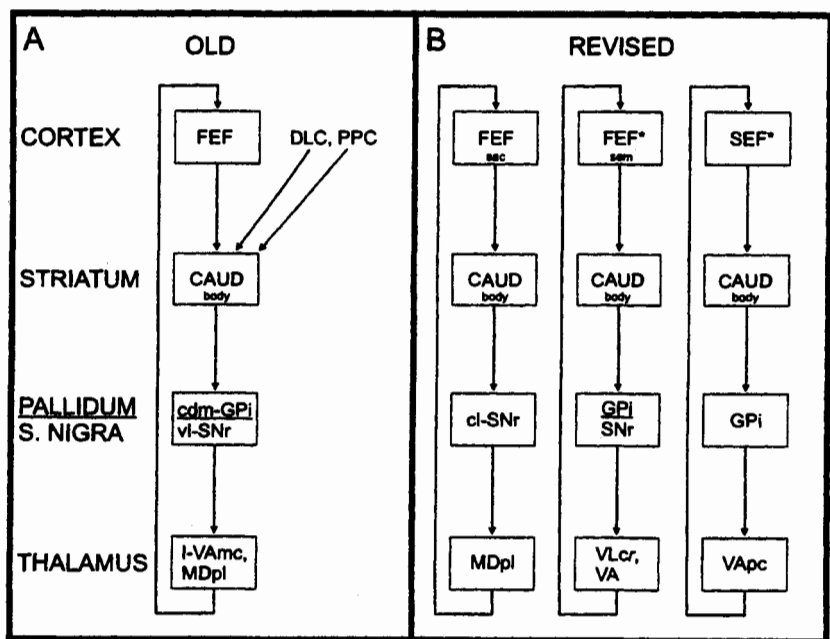

FIGURE 2.2. The original and revised oculomotor circuit. Conventions as in Figure 2.1. Additional cortical abbreviations: DLC, dorsolateral prefrontal cortex; FEFsac, frontal eye field, saccadic area; FEFsem, frontal eye field, smooth eye movement area; PPC, posterior parietal cortex; SEF, supplementary eye field. Additional basal ganglia abbreviations: CAUD, caudate; cdm, caudal dorsomedial. Additional thalamic abbreviations: l, lateral; MDpl, nucleus medialis dorsalis, paralaminar portion; VAmc, nucleus ventralis anterior, magnocellular division.

that each of the three oculomotor fields in the FEF and SEF is part of a separate basal ganglia loop (Figure 2.2B).

DORSOLATERAL PREFRONTAL LOOPS

In the original proposal (Alexander et al., 1986), Walker's area 46 was thought to be the principal target of basal ganglia output from the "dorsolateral prefrontal circuit." This circuit was believed to involve the dorsolateral regions of the head of the caudate, lateral dorsomedial portions of GPi/rostrolateral portions of the SNr, and thalamic neurons in the parvocellular portions of VA and MD (VApc/MDpc) (Figure 2.3A). In recent experiments, we performed a detailed analysis of basal ganglia outputs to regions of dorsolateral prefrontal cortex in portions of areas 9 and 46 (Middleton & Strick, 1994, 1997, 2000). We found evidence that the dorsolateral prefrontal circuit is actually composed of four output channels (see Middleton & Strick, 2000). The dorsal portion of area 46 (46d) is the target of a pallidal output channel that is located in a region of dorsal GPi, at rostral and middle levels of the nucleus. In contrast, ventral area 46
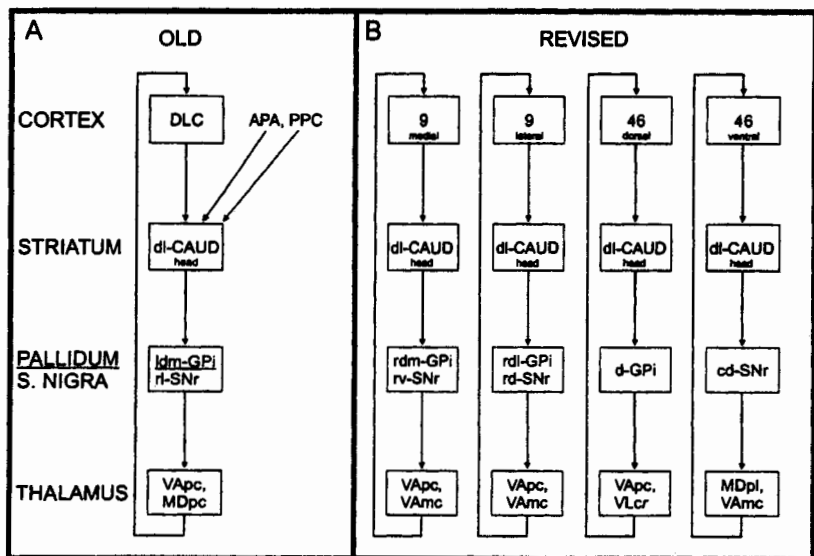

FIGURE 2.3. The original and revised dorsolateral prefrontal circuit. Conventions as in previous figures. Additional abbreviations: cd, caudodorsal; d, dorsal; dl, dorsolateral; ldm, lateral dorsomedial; rd, rostrodorsal; rdl, rostrodorsolateral; rdm, rostrodorsomedial; rl, rostrolateral; rv, rostroventral.

(46v) is the target of a nigral output channel that is located in caudal and dorsal regions of SNr. Separate output channels project to medial and lateral portions of area 9 (9m and 9l). In these cases, however, the output channels span GPi and SNr. Within GPi, the neurons that project to area 9m are located dorsal to those that project to area 9l. Within SNr, the neurons that project to area 9l are found dorsal to those that project to area 9m. Thalamic inputs to a dorsal portion of area 10 suggest that this region of prefrontal cortex may also be the target of basal ganglia output (Middleton & Strick, unpublished observation). Thus there are at least four, if not five, separate basal ganglia circuits involving regions of dorsolateral prefrontal cortex (Figure 2.3B).

LATERAL ORBITOFRONTAL LOOPS

Alexander and colleagues (1986) proposed area 12 as the cortical target of the lateral orbitofrontal circuit. In addition to area 12, this circuit was also thought to receive input from regions of the temporal and cingulate cortices. The portions of the basal ganglia involved in this circuit were believed to include the ventromedial head of the caudate, medial GPi/rostromedial SNr, and thalamic neurons in medial VAmc and MDmc (Figure 2.4A). We have examined the thalamic and basal ganglia inputs to different portions of area 12 with both viral and conventional tracers (see Middleton & Strick, 1997, 2000). These studies have shown that the lateral portion of area 12 (12l) is the target of a distinct output channel that originates in the caudomedial SNr and most likely passes through the multiformis portion of MD and VAmc (see also Barbas et al., 1991; Dermon & Barbas, 1994; Goldman-Rakic & Porrino, 1985). Similarly, conventional tracer studies of orbital area 12 (12o) indicate that it receives a prominent input from VAmc, but only minor input from VApc (Middleton & Strick, unpublished observation; Barbas et al., 1991; Dermon & Barbas, 1994; Goldman-Rakic & Porrino, 1985). The projection to 12o originates from a different region of VAmc than that which projects to area 12l. These results suggest that 12o and 12l are targets of distinct output channels from the nigra, but not GPi. Thus at this point at least two regions of lateral orbitofrontal cortex have the potential to participate in closed-loop circuits with the basal ganglia (Figure 2.4B).

MEDIAL ORBITOFRONTAL LOOPS

Basal ganglia loops may not be limited to the lateral part of orbitofrontal cortex. Alexander and colleagues (1986) included medial orbitofrontal loops within the "anterior cingulate circuit" (see below). However, we have chosen to list them separately here. As pointed out in the original proposal,
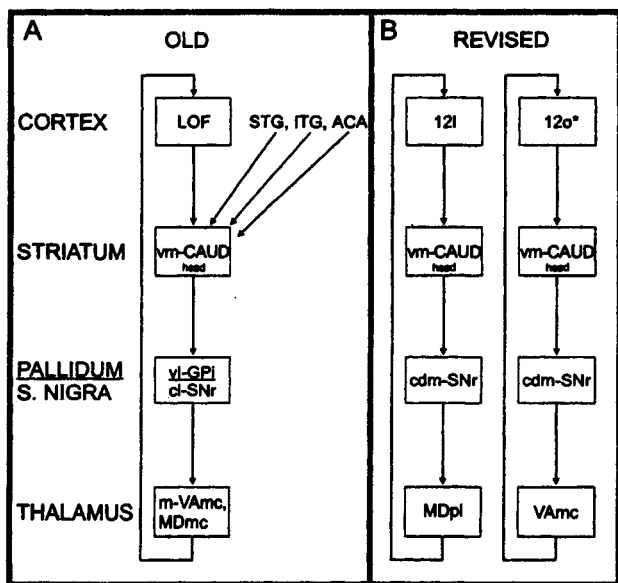
FIGURE 2.4. The original and revised lateral orbitofrontal circuit. Conventions as in previous figures. Additional abbreviations: ACA, anterior cingulate area; ITG, inferior temporal gyrus; LOF, lateral orbitofrontal cortex; m, medial; STG, superior temporal gyrus; vm, ventromedial; VP, ventral pallidum; VS, ventral striatum; 12l, lateral area 12; 12o, orbital area 12.

area 13 has projections to the ventromedial caudate and ventral striatum (Figure 2.5A). It also receives thalamic input from regions of VAmc and MD that are the targets of nigral efferents (Barbas et al., 1991; Dermon & Barbas, 1994; Goldman-Rakic & Porrino, 1985). In addition, VA/VL regions that receive nigral input are known to project to at least two transitional cortical areas that lie immediately caudal to area 13 (Dermon & Barbas, 1994). These areas have been termed the proisocortical (Pro) and periallocortical (Pall) regions by Barbas and colleagues (see Barbas et al., 1991), but have also become known as the lateral, intermediate, and medial agranular insular cortices (see Carmichael & Price, 1994). Importantly, each of these areas appears to have some projections to the input stage of basal ganglia processing. Thus closed-loop circuits may exist with multiple regions of the medial orbitofrontal cortex, including at least one neocortical and two transitional cortical areas (Figure 2.5B).

ANTERIOR CINGULATE LOOPS

The region of anterior cingulate cortex within area 24 was thought (Alexander et al., 1986) to participate in a basal ganglia loop involving the ven-
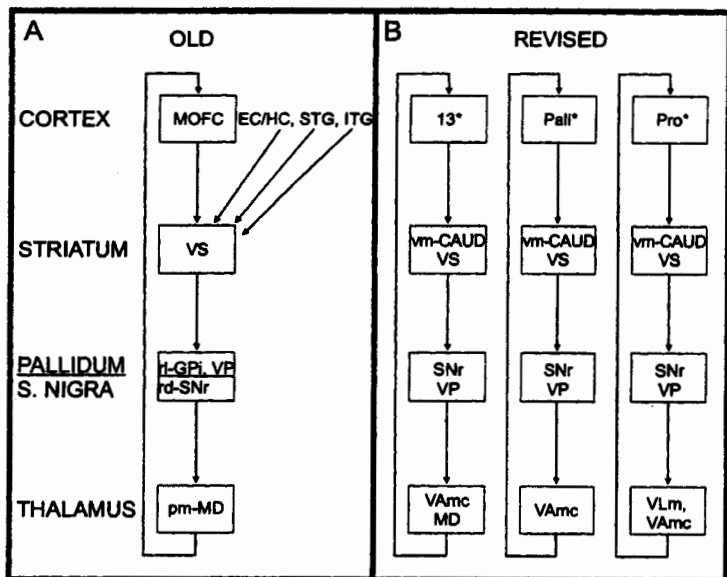
FIGURE 2.5. The original and revised medial orbitofrontal circuit (previously combined with anterior cingulate circuit [see Figure 2.6]). Conventions as in previous figures. Additional abbreviations: EC/HC, entorhinal cortex/hippocampal cortex; Pall, periallocortex; pm, paramedian; Pro, proisocortex.

tral striatum, rostrolateral GPi/ventral pallidum/rostrodorsal SNr, and thalamic neurons in medial MD (Figure 2.6A). This loop (along with the medial orbitofrontal) was said to constitute the "limbic circuit." The discovery of the motor areas in the cingulate sulcus (see "Skeletomotor Loops," above; see also Dum & Strick, 1991; He, Dum, & Strick, 1995; Picard & Strick, 1996) suggests alternative functional interpretations of basal ganglia circuits with anterior regions of cingulate cortex. For example, area 24 can be divided into at least three subdivisions: areas 24a and 24b, which lie on the cingulate gyrus, and area 24c, located in the ventral bank and fundus of anterior portions of the cingulate sulcus (see Dum & Strick, 1993; He et al., 1995). Area 24c contains the rostral cingulate motor area (CMAr), which projects directly to "M1" and the spinal cord. Intracortical stimulation in the CMAr produces movements of different body parts at relatively low thresholds. A careful review of the anatomical literature suggests that regions of the ventrolateral thalamus that receive basal ganglia efferents send projections to area 24c, but not areas 24a and 24b. This suggests that the output of the basal ganglia is directed at the CMAr, and not the cingulate gyrus proper. Thus this circuit may be more closely related to motor than to limbic function.

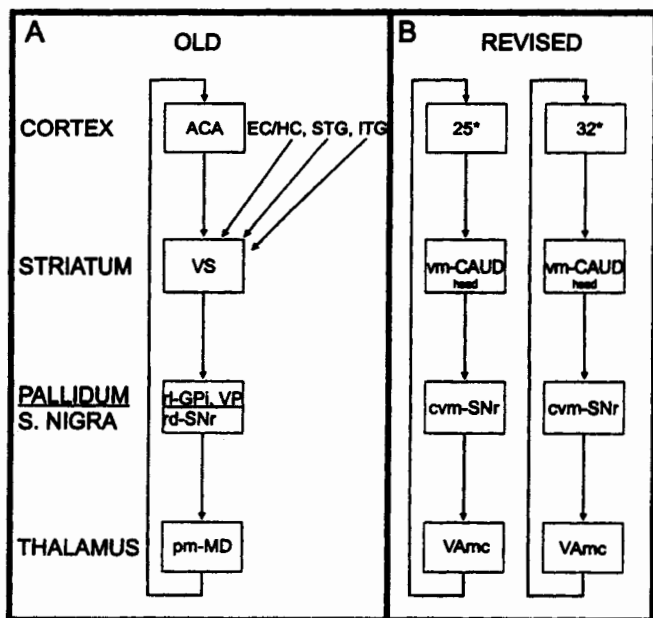On the other hand, the anatomical substrate may exist for basal ganglia

FIGURE 2.6. The original and revised anterior cingulate circuit. Conventions as in previous figures. Additional abbreviation: cvm, caudal ventromedial.

loops with more anterior and ventral regions of cingulate cortex. Portions of area 25 and possibly adjacent portions of area 32 receive a sizeable component of their input from regions of VA/VL that are the targets of nigral efferents (Barbas et al., 1991; Dermon & Barbas, 1994). There is considerable evidence from studies in humans and nonhuman primates that these regions of the anterior cingulate cortex play an important role in modulating emotional function and autonomic arousal (see Vogt & Gabriel, 1993). Thus it is possible that the SNr has an influence on emotional function through output channels to these cortical areas (Figure 2.6B). Some support for this suggestion comes from the recent observation that stimulation near SNr in a patient with Parkinson's disease evoked a major depressive episode. Thus abnormal activity in basal ganglia circuits with areas 25 and 32 may contribute to mood disorders in patients with basal ganglia dysfunction.

INFEROTEMPORAL/POSTERIOR PARIETAL LOOPS

In the past, many cortical areas outside of the frontal lobe were thought to project to the input stage of basal ganglia processing, but none of these ar-

eas were known to be the targets of basal ganglia output (Alexander et al., 1986; Kemp & Powell, 1971). Cortical areas outside the frontal lobe were thought to utilize basal ganglia circuits for feedforward processing that would enable them to influence the executive functions of the frontal lobe. However, our review of the anatomical literature indicates that a number of cortical areas outside of the frontal lobe may receive input from thalamic nuclei that are the targets of nigral efferents (for references and reviews, see Jones, 1985; Middleton & Strick, 1996). Indeed, using viral tracing techniques, we demonstrated that area TE in inferotemporal cortex (see Gross, 1972) is the target of a distinct output channel from SNr (Middleton & Strick, 1996). Based on the patterns of thalamocortical connections, similar output channels may exist with other nonfrontal regions of the cerebral cortex, including other areas of inferotemporal/ventral prestriate cortex, as well as regions of posterior parietal/dorsal prestriate cortex (see Middleton & Strick, 1996).

SYNTHESIS AND CONCLUSION

We have briefly reviewed some of the new anatomical information that has become available regarding the organization of basal ganglia circuits with the cerebral cortex. These data support many aspects of the original model proposed by Alexander and colleagues (1986). In addition, it is now clear that more cortical areas are the targets of basal ganglia output than were originally proposed. Many of the cortical regions that were thought to be merely sources of afferents to the input stage of basal ganglia processing are now known to be the targets of efferents from the output stage of basal ganglia processing. Indeed, basal ganglia circuits clearly extend beyond their traditional territory of the frontal lobe and include loops involving inferotemporal/ventral prestriate and possibly posterior parietal cortex. As described above, the five original "circuits" should be expanded to seven general categories: skeletomotor, oculomotor, dorsolateral prefrontal, lateral orbitofrontal, medial orbitofrontal, anterior cingulate, and inferotemporal/ posterior parietal. Importantly, each of these categories is comprised of multiple parallel segregated circuits.

A complete review of the physiological and behavioral data on basal ganglia circuits is beyond the scope of this presentation. However, we would like to emphasize two important functional implications of the anatomical arrangement we have described. The output of the basal ganglia is capable of influencing a vast range of behavior through its projections to multiple areas of the cerebral cortex. Indeed, as the list of cortical areas that participate in basal ganglia circuits grows, the repertoire of basal ganglia functions will increase in richness as well. As a consequence, widespread damage to the basal ganglia can produce a broad array of dys-

functions that involve motor, cognitive, limbic, and sensory domains (see Alexander et al., 1986; Bhatia & Marsden, 1994; Cummings, 1993; Middleton & Strick, 2000). On the other hand, the highly topographic and closed-loop nature of basal ganglia connections means that each individual circuit may be concerned with very specific functions related to the cortical area that participates in the circuit. As a result, localized damage to the basal ganglia can have consequences that are limited to a single functional domain or even a single body part (see Alexander et al., 1986; Bhatia & Marsden, 1994; Cummings, 1993; Middleton & Strick, 2000). Thus understanding the basic anatomical organization of basal ganglia loops with the cerebral cortex provides a critical foundation for exploring the functional contributions of these circuits.

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