CHAPTER 28

The Contribution of Anterior Cingulate-Basal Ganglia Circuitry to Complex Behavior and Psychiatric Disorders

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Chapter contents

The rostral cingulate cortex consists of at least three major functional domains, which subserve distinct but complementary roles in guiding behavior. Two of these domains exist as separate anatomical regions—the anterior cingulate cortex (ACC), which is specialized for the processing of limbic, autonomic, and reward-related information, and the midcingulate cortex (MCC), which receives nociceptive inputs and engages in the regulation of movement via the cingulate motor areas (CMAs). The third cingulate domain is not anatomically distinct, but exists as a higher-order domain that integrates signals from prefrontal areas concerned with working memory and the signals to motor and premotor areas involved in motor outputs, and thus can be said to be involved in the *selective* guidance of behavior to achieve intended outcomes. In this sense, the third domain encompasses the most complex forms of behavior represented in cingulate cortex.

At the cortical level, the involvement of the rostral cingulate cortex in both simple and complex behavior has been demonstrated in various functional imaging paradigms and even with intracortical stimulation and single unit recording. It is important to recognize, however, that such activations are dependant to a large extent on the anatomical connections that exist between the cingulate cortex and other cortical and subcortical regions. The focus of this review is on the cingulate connections with the group of subcortical nuclei termed the basal ganglia. In the past, such connections were viewed solely as a way for limbic regions of cortex to influence motor outputs. We now know, however, that rather then serving as a point of convergence, cingulate-basal ganglia connections consist of multiple circuits that either project back to the same cortcial region that they originate in (closed-loop circuits) or display widely divergent influences on other circuits (open-loop circuits). By extension, disruption of these circuits, at either the cortical or subcortical level, has the potential to lead to alterations of both single and multi-component behaviors.

Goals of This Chapter

In this review, the distinctions in the cortical and subcortical connections between the three cingulate domains, concerned with emotional control, motor control, and attention and working memory, will be evaluated. Particular emphasis will be placed on the role of the cingulate-basal ganglia circuitry in modulating simple and complex functions. Obsessive–compulsive disorder (OCD) will be used as a primary example of how disruption of the newly-defined cingulate-basal ganglia circuitry can lead to the development of a syndrome with limbic, motor, and higher-order manifestations. The lessons from this example could have broad application to other neuropsychiatric disorders known to affect the cingulate cortex, including schizophrenia, major depression, and attention-deficit hyperactivity disorder.

Anterior Cingulate Cortex Connections with the Prefrontal Cortex

The prefrontal cortex (PFC) and rostral cingulate cortex sit at the apex of a hierarchy of cortical areas that regulate the most advanced functions of the primate brain—cognition, planning, reasoning, verbal skills, and working memory. Although these areas play an essential role in these functions, they do not do so in isolation. Rather, the PFC and cingulate cortex rely heavily on upstream and downstream cortical and subcortical areas to exert this influence. On the sensory input side, the PFC is generally regarded as the last weigh station of both the dorsal and ventral stream of visual processing. For example, the dorsal PFC receives considerable input from the lateral parietal cortex areas concerned with attending to the spatial aspects of visual cues (Cavada & Goldman-Rakic, 1989; Petrides & Pandya, 1999). In contrast, the ventral PFC receives considerable input from inferotemporal areas concerned with discriminating colors and features of visual stimuli. Importantly, the diversity of sensory inputs to the PFC is not limited to visual modalities, and includes auditory, somatosensory, gustatory, and olfactory inputs as well. Why does the PFC receive these diverse inputs? It is now accepted that the PFC actually stores much of the information it receives in working memory for use in the performance of goal-directed or rule-based behaviors (reviewed in Fuster, 2001). Thus, the PFC is said to be critical for spatial, object, verbal, and sequential working memory task performance. However, it is important to keep in mind that the PFC does not itself have direct control over the cells that regulate the movements and muscles required to produce such goal-directed behaviors. Rather, the PFC must somehow influence other cortical and subcortical areas to indirectly effect responses. At the cortical level, this control is possible through an extensive array of connections that the PFC has with several premotor areas of cortex—particularly the frontal and CMAs (Bates & Goldman-Rakic, 1993; Lu *et al.*, 1994).

In non-human primates, the CMAs lie within the MCC and include the portions of area 24' that lie on the dorsal and ventral banks of the rostral cingulate sulcus (Dum & Strick, 1993; see Chapter 3 for a complete comparative discussion in human and non-human primates). By standard definition, each of these premotor areas has a topographic representation of parts of the body mapped out, has the capacity to produce movements of those particular body parts when stimulated

at low thresholds, and has direct projections to the primary motor cortex and ventral horn of the spinal cord (Dum & Strick, 2002). Moreover, stimulation of the human MCC appears capable of producing highly complex, stereotyped movements that involve multiple body parts (Talairach *et al*., 1973). Activation of the MCC is clearly seen during motor tasks that involve single body parts, multiple body parts, or the learning of new sequences of movements. In addition to the CMAs, regions of the PFC involved in working memory are also highly interconnected with regions of the ACC and MCC that are not directly involved in motor control. These areas of the cingulate are usually activated during some of the same cognitive tasks that rely on the dorsolateral PFC (such as the Stroop test, Pardo, 1990) and rule-based verb-generation task (Petersen & Fiez, 1993). This common pattern of activation may be related to the selective guidance of attention required to complete such tasks or inhibit the natural (erroneous) responses on such tasks. Thus, at the cortical level, the PFC gains fairly rapid and robust access to cingulate areas regulating both simple motor functions and two types of complex motor functions—those involving the selection of correct responses based on reward or saliency information, and those involving the coordination of multiple body parts.

Cingulate-Subcortical Circuitry

While the PFC and multiple regions of the ACC and MCC interact strongly at the cortical level, there appears to be much less evidence for their interaction in the subcortical circuits they participate in. The subcortical circuits that are a focus of this review are those with the basal ganglia. Animal lesion and human clinico-pathological studies established over a century ago that damage to the basal ganglia results in characteristic motor symptoms and deficits. The majority of these deficits are believed to be due to interruption of basal ganglia connections with motor areas of cortex. It will be suggested here that some of the complex motor abnormalities seen following basal ganglia damage may be due to disruption of circuits with the CMAs in the MCC, while other alterations (including emotional dysfunction) may be due to disruptions of basal ganglia circuits with the subgenual ACC (sACC). In order to provide a framework for this discussion, the connections between the rostral cingulate cortex and the basal ganglia are first described.

Closed Loops with the MCC and ACC

In the simplest terms, the connections between the cerebral cortex and basal ganglia can be described as consisting of a set of input structures, that receive direct or second-order projections from the cerebral cortex, and a set of output structures, that project back to the cerebral cortex via the thalamus. The input structures of the basal ganglia include the subthalamic nucleus and the striatum, the latter of which can be divided into the ventral striatum (which includes the nucleus accumbens) and the dorsal striatum (which includes the putamen and caudate). The output structures of the basal ganglia include the internal segment of the globus pallidus (GPi), the ventral pallidum (VP), and the substantia nigra pars reticulata (SNpr). As a result of the reciprocal connectivity between the basal ganglia structures and the cortex, the basal ganglia are said to participate in feedback loops with the cerebral cortex. Within these connections, the shortest path through the basal ganglia is referred to as the 'Direct path', while a path containing at least one additional connection is termed the 'Indirect path' as shown in Figure 28.1. In addition, it is now recognized that a third 'Subthalamic path' exists, originating throughout much of the frontal lobe. As we shall see, these three different sets of paths appear to form closed feedback loops with the cingulate cortex.

According to Selemon and Goldman-Rakic (1985), widespread regions of the ACC project to the ventromedial caudate and ventral striatum. The ACC shares this pattern of striatal inputs with at least two other subcortical areas that it is connected with, including the amygdala and hippocampal formation (Morecraft & Van Hoesen, 1993). Similar robust and topographically organized patterns of inputs to the basal ganglia have also been seen to arise from portions of the MCC that include the CMAs. Thus, it can certainly be concluded that limbic and skeletomotor regions of the rostral cingulate cortex gain access to the basal ganglia. In the past, according to the classical concept of the 'limbic motor system' it was thought that these cortical inputs enabled the basal ganglia to integrate the information they received from widespread areas of the cerebral cortex and 'funnel' this information into the motor system to direct the commands for movement (Evarts & Thach, 1969). More recent information, however, has clearly established that much of the cortical–subcortical loops that can be identified consist of topographically segregated parallel circuits (Alexander *et al*., 1986; Middleton & Strick, 2000a,b).

Based on their early analysis of striatal and thalamic connections with different cortical areas, DeLong and Georgopoulos (1981) first proposed that basal ganglia loops with the cerebral cortex could be broadly divided into those with motor functions and those with non-motor functions. Alexander *et al*. (1986) expanded on this idea and proposed the existence of basal ganglia closed-loop circuits with three non-motor regions of the PFC:, the dorsolateral PFC (area 46),

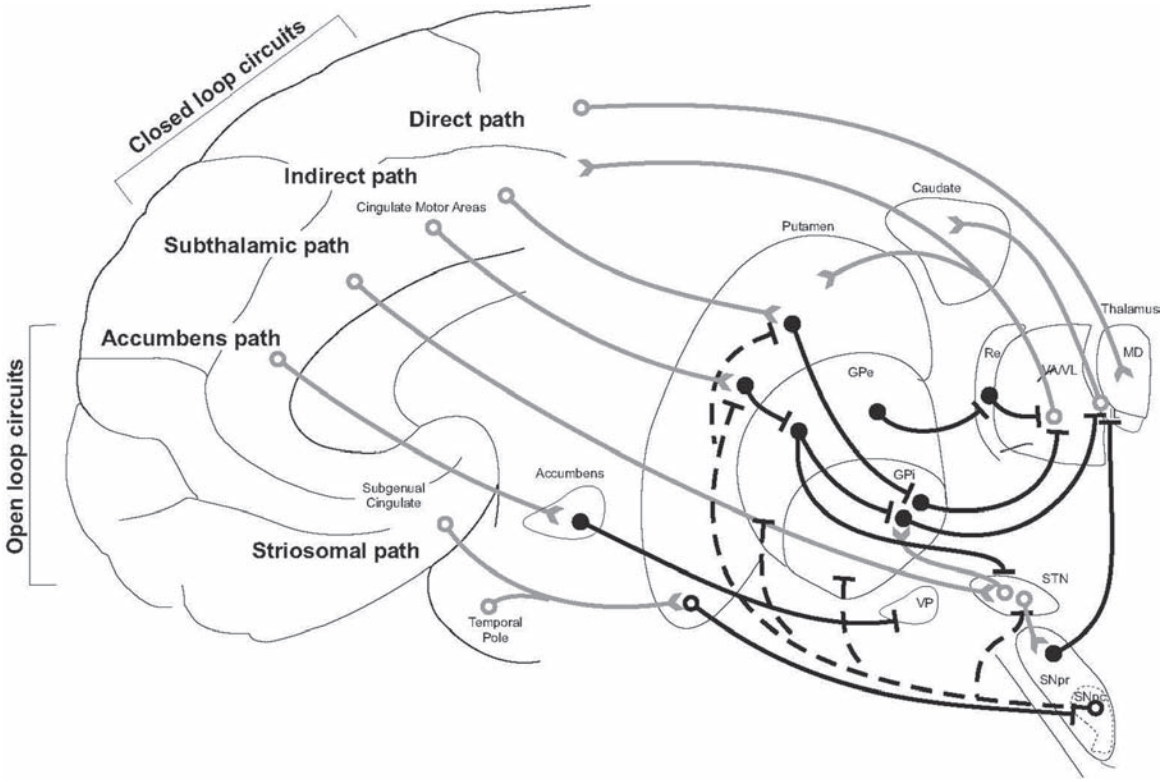

Fig. 28.1 Basal ganglia circuits with the rostral cingulate cortex. The vast majority of the MCC (and a small component of the ACC) participate in recurrent closed-loop circuits involving the Direct, Indirect, Subthalamic and Accumbens pathways, while an open-loop circuit involving the striosomal pathway best characterizes the interconnections between the ACC and basal ganglia. GPe, external globus pallidus; GPi, internal globus pallidus; MD, mediodorsal nucleus; Re, reticular nucleus; SNpc, substantia nigra pars compacta; SNpr, substantia nigra pars reticulata; VA/VL, ventroanterior/ventrolateral nuclear complex; VP, ventral pallidum.

the lateral orbitofrontal cortex (area 12), and the 'anterior cingulate' and medial orbitofrontal cortices (areas 24 and 13). The latter of these cortical areas were envisioned as part of a 'limbic' circuit that passed through the ventral striatum, the GPi, VP and SNpr, and the magnocellular division of the mediodorsal nucleus of the thalamus.

Past studies have shown that the ACC is the target of neurons in VA and MD that may be the target of GPi and SNpr (Nauta & Mehler, 1966; Kievit & Kuypers, 1977; Kuo & Carpenter, 1973; Percheron *et al*., 1996; DeVito & Anderson, 1982; Goldman-Rakic & Porrino, 1985). More recent studies have also established comprehensive profiles for the pattern of thalamic inputs to the more caudal CMAs in the MCC, from basal ganglia recipient regions of the thalamus (Table 28.1). Based on these studies, it is now plausible to revise the scope of basal ganglia loops to more correctly describe their involvement in simple and complex behavior mediated by the ACC and MCC.

Specifically, according to the additional information listed in Table 28.1, it does not seem accurate anymore to consider the 'limbic circuit' with the basal ganglia as a single entity envisioned by Alexander *et al*., (1986) or their predecessors. Rather, there appears to be a clear anatomical substrate for two types of closed-loop cingulate-basal ganglia circuits—those which subserve motor function and involve the rostral and caudal CMAs in the MCC, and those which subserve non-motor function and involve ACC areas 24a′/b′, 25 and 32 as shown in Figure 28.2. This is a major departure from the previous models that characterized cingulate-basal ganglia closed-loop circuitry only in terms of unitary limbic function. Moreover, based on comparisons of the density of thalamic inputs to the MCC and ACC, it seems reasonable to conclude that *among the closed-loop circuits*, those subserving skeletomotor function are more robustly connected than those subserving limbic function.

Exceptions to Closed Loops: Open Loops and the ACC

Even though there are a large number of circuits in the basal ganglia that appear to operate in parallel with each other, and via closed feedback loops, these circuits are

TABLE 28.1 Closed-loop thalamic inputs to the rostral cingulate cortex in non-human primates

	Area	VAmc	VLm	rMDpl	VApc	rVLc	VLo	CM/Pf	References
MCC	CMAr	–	+	++	+++	+/–	++	++++	1, 3, 7, 9
	CMAv	–	+	+	+	+	++++	++	1, 3, 7, 9
ACC	24a'/b'	+/++	–	–	+	–		–	2, 4, 5, 8
	25	+++++	++	?	+	–		–/+	8, 5
	32	+/++	–/+	–/+	–/+	–		+	4, 5, 6, 8
				Nigral Targets				Pallidal Targets	

ACC, anterior cingulate cortex; MCC, midcingulate cortex.

Cells per 'hotspot' section or % of cells

+	10–Jan
++	20–Nov
+++	21–30
++++	31–40
+++++	More than 40

Reference

1 Dum & Strick (1993)
2 Goldman-Rakic & Porrino (1985)
3 Morecraft *et al.* (1993)
4 Vogt *et al.* (1987)
5 Yterian & Pandya (1988)
6 Barbas *et al.* (1991)
7 Van Hoesen *et al.* (1993)
8 Demon & Barbas (1994)
9 Hatanaka *et al.* (2003)

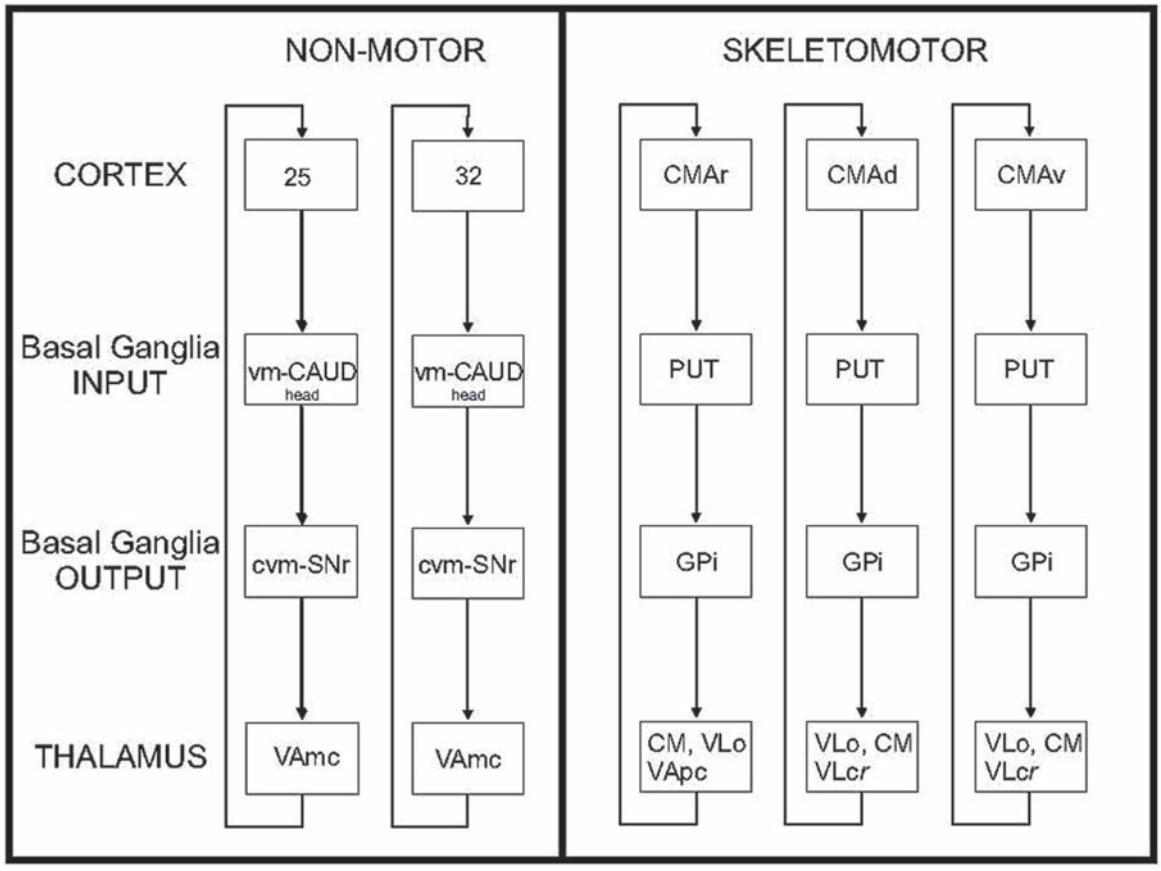

Fig. 28.2 Cingulate-basal ganglia closed-loop circuits. At least two separate regions of the ACC and MCC demonstrate clear patterns of connections with the basal ganglia input and output nuclei (via the thalamus) to be considered as participating in closed-loop circuits. CM, centromedial nucleus; CMAr, rostral cingulate motor area; CMAc, caudal cingulate motor area; cvm-SNr, caudoventromedial substantia nigra pars reticulata; VAmc, ventral anterior nucleus, magnocellular division' VApc, ventral anterior nucleus, parvocellular division; VLc*r*, rostral division of the ventrolateral pars caudalis nucleus; VLo, ventral lateral pars oralis nucleus; vm-CAUD, ventromedial region of the caudate.

not without some degree of cross-circuit influences, and not all circuits provide feedback to the same cortical area that they originate in. One of the most striking examples of such open-loop components involve the connections that are known to relay reward-related information, and form what is referred to as the 'Striosomal path' (Fig. 28.1). The Striosomal path is primarily composed of inputs from limbic regions of the anterior temporal pole and the sACC. Rather than project to the striatal matrix as most other neocortical projections contributing to the closed-loop circuits do, these cortical areas innervate the striosomes, which are acetylcholinesterase-poor zones in the striatum (Eblen & Graybiel, 1995). The projection neurons in the striosomes and matrix have completely different targets. Projection neurons in the matrix participate directly in the classic closed-loop circuits subserving motor and cognitive function through projections to the GPi and SNpr (Fig. 28.1). In contrast, the striosomal projection neurons project almost exclusively to the dopaminergic (pars compacta) neurons of the substantia nigra (SNpc) (Fig. 28.1). The neurons in the SNpc, in turn, project back upon the vast majority of the entire striatal matrix. In this manner, any limbic and/or motivational information received by the basal ganglia from the sACC or temporal pole that innervates the striosomes can influence any or all of the different circuit types in the basal ganglia, via modulation of dopaminergic (DA) inputs to those circuits.

Another major open-loop component of the ACC circuitry appears to take the form of the 'Accumbens path' (Fig. 28.1). The ACC inputs to the accumbens are derived from largely areas 24a′/b′ and 32 (which also innervate the ventromedial caudate and contribute to closed-loop circuitry). The accumbens, in turn, projects to brain stem nuclei such as the pedunculopontine nucleus, as well as the VP. In rodents, the VP projects back to the MD nucleus of the thalamus. However, in primates, there appears to be only a very weak projection from VP to MD. Thus, based on the paucity of recurrent feedback projections, it is probably more appropriate to conceptualize the Accumbens path as more of an open-loop circuit than a closed-loop circuit.

Given the massive inputs to the striosomes from the ACC and temporal pole, to understand how these loops might function, it is helpful to consider the nature of the information that is being conveyed from the ACC to the nigrostriatal system. It has become increasingly clear of late how profound the reward or context-dependent modulation of the SNpc neurons (and the striatal neurons they innervate) can be. For example, the SNpc cells themselves do not display changes in activity in relation to simple or complex movements, except under the situation where the particular movement is associated with the receipt of a reward, or the expectation of receiving a reward. By virtue of their diverse influences in the striatum, such integrated stimulus-response-reward information would have the potential to drive meaningful behavior of multiple different circuits. In a similar manner, cells in the striatum have also been observed to show striking stimulus-response associations that are strongly influenced by reward. The giant cholinergic interneurons (also called tonically active neurons) normally do not display moment to moment changes in behavior, until an association is built between a specific stimulus and response that leads to behavioral reinforcement. These neurons comprise a very small percentage of the cells in the striatum, but have very long arborizations that interconnect neurons in different functional circuits. The properties of cells in the striatal matrix that participate in closed-loop circuits are themselves influenced by these giant cholinergic interneurons as well as the nigrostriatal dopaminergic inputs they receive, and these neurons display perhaps the most striking reward-dependent modulation (reviewed in Middleton, 2003). Indeed, while striatal neurons can be described which are tuned to particular movements or stimulus directions, large numbers of these cells have recently been described as completely reversing their preferred tuning directions if movements to the opposite direction are rewarded. This reversal is believed to be modulated in large part by the midbrain dopaminergic influence on the striatum, which have recently been shown to show decreased activity in non-rewarded trials (Kawagoe *et al.*, 2004). Thus, in summary, the Striosomal path clearly appears positioned to help drive the behaviors most associated with positive reward.

Open- and Closed-Loop Circuits in Complex Behaviors and Psychiatric Disorders

Most of the clinical and pathological reports of patients with basal ganglia damage indicate that these patients display a number of different symptoms, including both motor and non-motor ones and it is likely that these symptoms are due to involvement of several adjacent subcortical fiber systems or loops (Alexander *et al.*, 1986; Cummings, 1993). Even patients with 'isolated' lesions of the globus pallidus, experience both motor and cognitive deficits such as working memory, card sorting difficulties, compulsive behaviors, and "psychic akinesia" (lack of a desire to move). Interestingly, some patients with Parkinson's disease and Huntington's disease are also impaired on various tests of sequence learning and sequential task performance as well as aspects of spatial and non-spatial working memory and the performance of rule-based tasks, often prior to the development of severe motor symptoms (see Middleton & Strick, 2000a,b for additional references and review). Since many of these same functions are subserved by the PFC and ACC, they could be due to disruption of circuits with these areas.

Given these background data, it is perhaps not surprising that there is growing evidence that alterations in basal ganglia output to the ACC may occur in a wide range of psychiatric disorders such as schizophrenia, depression, OCD, Tourette's syndrome, autism, and attention deficit/hyperactivity disorder (ADHD). Each of these disorders has been associated with structural or metabolic changes in the basal ganglia, as well as alterations in areas of the PFC connected with the ACC. Indeed, since the proposal of Alexander *et al.* (1986), numerous models have been proposed for the involvement of PFC and ACC circuits with the basal ganglia in many of these disorders, in addition to Parkinson's and Huntington's diseases (Table 28.2). Many of these models clearly contain elements that need to be revised based on a more current understanding of the anatomical and functional connectivity of the ACC, MCC, and the basal ganglia, but they are good starting points nonetheless. In the section that follows, a revised model of cingulate-basal ganglia circuitry involvement in OCD will be presented.

A Revised Theory of Cingulate Cortex-Basal Ganglia Circuitry in OCD

Obsessive–compulsive disorder is a complex behavioral disorder characterized by persistent obsessive thoughts and compulsions to act on those thoughts. In the absence of acting on those compulsions (i.e., ritualizing), subjects with OCD display considerable anxiety and emotional lability. To set the stage for revising theories about the involvement of ACC-basal ganglia circuitry in OCD, it is useful to briefly review the activation patterns that have been reported in previous studies.

What cingulate areas are active in OCD?

Very few studies have reported imaging findings in Talairach or stereotaxic coordinates (but see Rauch *et al*, 1994, and others). These, together with some additional studies show specific areas of activation in orbitofrontal cortex, as well as portions of the ACC and MCC after symptom provocation. Such areas include what appear to be portions of areas 47 and 45 on the lateral surface of the cortex, portions of areas 11 and 12 on the orbital surface, and several regions of cingulate cortex: areas 25, area 24 and 32 anteriorly, the arm region of the anterior portion of the rCMA, portions of area 24 on the edges of the arm region of the cCMA, and the thalamus (Fig. 28.3).

An important point to consider in these studies is the methods of symptom provocation and the particular profiles of the patients. Most of them had hand washing rituals and obsessive thoughts about contamination. Their symptoms were provoked while lying in a PET scanner by the examiner placing a glove or other object on the patients arm and telling them it was a dirty glove (e.g., had blood or feces on it). Such stimulation has at least three immediate effects on these patients. First, they think obsessively about the glove and its contaminants. Second, they experience a strong emotional sensation such as anxiety, fear, or unhappiness at being contaminated. Third, they begin to imagine washing their hands or a similar ritual that would decontaminate them. Here, it is suggested that such a three stage process (of ideation, emotion, and ritualization) could be represented at the cortical level by three separate regions. This raises the question of whether these three effects of OCD symptom provocation can be explained in light of studies of brain activation during ideation (object working memory), emotion (anxiety or unhappiness), or intended action (self-generated hand movements)?

Are studies of ideation consistent with the OCD findings?

It is now apparent from a number of labs that portions of the temporal lobe and inferior PFC (areas 45, 46, 47 and 12) are involved in a working memory for objects. Some of the inferior frontal regions are also involved in verbal working memory. A number of these peak activation sites are near peak activation sites for OCD patients that have been reported on the lateral surface. This observation may be consistent with an OCD patient obsessively thinking about a contaminated glove and perhaps vocalizing the words dirty, blood, feces, or other things to himself. Thus, it may be possible to consider the lateral orbitofrontal cortex and temporal lobes as centers for ideation. Studies in non-human primates are consistent with this observation. Lesions of lateral area 12 (similar to human area 47) cause the most severe perseverative responses on delayed object alternation and object working memory tests, and the neurons in area 12 appear to be tuned to the memory of particular objects over short delay periods. Similar effects are also produced from lesions or cooling of the anterior inferior temporal lobe.

Are reported activations in OCD consistent with activation during studies of depression, anxiety or unhappiness?

A growing number of studies have reported brain activations during depressed or unhappy states (Chapter 24; Drevets *et al*, 1992), or provoked anxiety (Gottschalk *et al*, 1992; Wik *et al*, 1991). The sites of activation in these patients are consistently found in similar areas: the lateral and medial surfaces of area 10 and a somewhat continuous band of activations from area 25 on the medial wall to the anterior cingulate gyrus including areas 24 and 32 (Fig. 28.3). The reported changes on the lateral prefrontal surface may reflect ideation about depressive objects or episodes. Some of the cingulate

TABLE 28.2 Early proposals of ACC-basal ganglia circuit involvement in neuropsychiatric disorders

Disorder	References	Hypothesis
Schizophrenia	Swerdlow and Koob (1987)	Excess activation of dopamine (DA) neurons projecting from the ventral tegmental area (VTA) to striatum results in reduced GABA projections from striatum to VP, and overactive GABA projections from VP to MD of thalamus. This causes interruption of thalamocortical feedback to cingulate/limbic cortex which results in an inability to filter inappropriate cognitive or emotional processes at striatal level, and an inability to select and maintain appropriate processes among corticothalamic interactions.
	Csernansky *et al.* (1991)	Defect of limbic cortex cytoarchitecture leads to an increase in excitatory cortico-ventral striatal (VS) activity, a reduction in VTA DA transmission to VS, and increased activity of GABA projections to frontal cortex. Over time, the decreased DA leads to increased D2 receptor density and sensitivity. When DA is acutely increased in this circuit in response to stress, there is a reduction in inhibitory pallidal output which leads to psychosis.
	Walker (1994)	Hyperactive DA transmission within anterior cingulate/limbic circuit is caused by excess D2 receptor density in VS or reduced glutamate excitation from cortex. This results in a reduction of indirect excitatory inputs to the VP and GPi/SNr, which disinhibits thalamocortical circuits and leads to psychotic symptoms.
	Carlsson and Carlsson, 1990	DA and glutamate projections to the striatum, as well as cholinergic interneurons in the striatum, act on the pallidal output neurons to facilitate meaningful behavior by suppressing irrelevant cortical impulses and their associated locomotor programs. In schizophrenia, increased DA metabolism and decreased glutamate metabolism interfere with this process.
Obsessive compulsive disorder (OCD)	Modell, *et al.* (1989)	The ventromedial portions of the caudate, VS, and pallidum provide a negative feedback on orbitofrontal areas. OCD symptoms occur when an aberrant positive-feedback loop develops in the reciprocal excitatory connections between the frontal cortex and thalamus, which are inadequately inhibited by the orbitofrontal circuit.
	Wise and Rapoport (1989)	The basal ganglia are a site for storage of motor programs and for gating of sensory input. Inputs to the basal ganglia from anterior cingulate/orbitofrontal cortices and the raphe nucleus project to a site in the pallidum that is an internal motivation detector. Sensory inputs from the temporal lobe converge on this same site in the pallidum after being processed by a striatal stimulus detector, or pattern recognition unit. This allows sensory and motivational factors to inhibit pallidal discharge and thus release motor programs in the thalamo-cortical pathways. If excess activity in the cingulate/orbitofrontal circuit occurs without sensory input, then repeated motor programs are continually released and OCD symptoms become evident.
	Baxter (1992)	The orbitofrontal cortex may be the locus of pathologic dysfunction. Outputs from the orbitofrontal cortex drive OCD-relevant circuits in the caudate, thus increasing inhibitory output to relevant regions of the globus pallidus. This reduces inhibition of the thalamus and allows it to be driven by the orbitofrontal cortex as well, thus producing a self-sustaining positive-feedback circuit.
	Cummings (1993)	The mania, irritability, and disinhibition seen in patients with OCD are the result of disruption of the structures within the orbitofrontal-basal ganglia circuit.
Tourette's syndrome (TS)	Anderson *et al.* (1992)	TS symptoms may be the result of compromised glutamate projections from the subthalamic nucleus (STN) to GPe and GPi/SNr with a resulting overactivity in thalamo-cortical activity.
	Stoetter *et al.* (1992)	In TS, normally separate orbitofrontal/limbic and sensorimotor circuits are somehow 'cross-wired' or 'short-circuited' at sites of limited convergence such as the substantia nigra. This results in VS activity being positively correlated with sensorimotor cortex activity and putamen activity being correlated most with orbitofrontal, hippocampal, amygdala, and temporal lobe activity.
Mood disorders	Mayberg (1993)	The mood disorders that have been documented in PD, HD, and patients with basal ganglia strokes are the result of: (1) primary cell loss in the frontal cortex; (2) remote changes in basotemporal limbic regions; (3) anterograde or retrograde disruption of basal ganglia-thalamo-cortical circuits from caudate degeneration or injury; and (4) degeneration of mesencephalic monamine neurons and their cortical and basal ganglia projections.
	Cummings (1993)	Mania, irritability, and disinhibition are the result of disruption of the structures in the orbitofrontal basal ganglia circuit. Apathy is the cardinal symptom of disruption of the structures in the anterior cingulate-basal ganglia circuit. Depression can result from disorders of the dlPFC basal ganglia circuit.

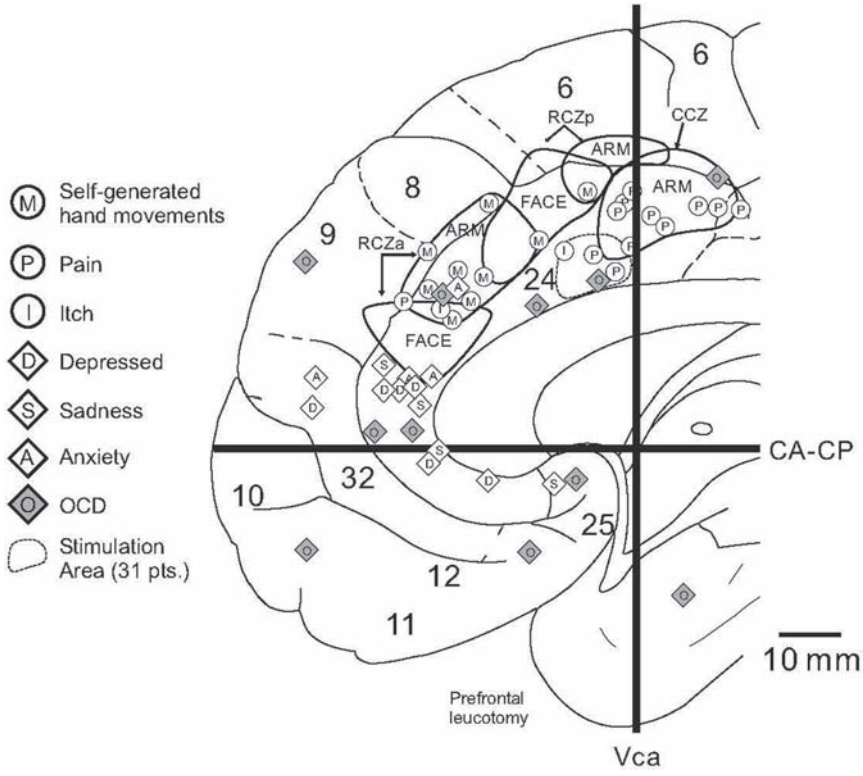

Fig. 28.3 Cingulate activations in obsessive–compulsive disorder (OCD) and related behavioral tasks. Points shown indicate peak foci (Talairach coordinates) replotted from a series of studies discussed in the text. Adapted from Picard and Strick (1996).

activations are near the face area of the anterior portion of the rCMA (Fig. 28.3). This would correlate well with the observation that during anxiety symptom provocation, the jaw muscles are much more active, as subjects tend to clench their teeth. Thus, these studies suggest that the medial orbitofrontal and rostral/sACC are involved in the control or expression of emotions such as anxiety, depression, or sadness. Lesion studies in monkeys provide some support for this in that the separation calls of monkeys are eliminated by large lesions of area 25 (MacLean and Newman, 1988), but leave the animal otherwise able to vocalize.

Are activations of the cingulate motor areas during self-paced hand movements consistent with the urge to wash the hands (ritualize), or even to scratch or move the hands?

Strong evidence indicates that this may be the case (see Picard & Strick, 1996; Fig. 28.3). Specifically, the studies by Playford *et al.,* (1993) and Frith *et al.,* (1991) both involved random finger or joystick movements and both produced sites of peak activation near the sites of OCD symptom provocation in studies by Rauch and others. In addition, the urge to scratch study by Hsieh *et al.,* (1994) produced activation in or near two of the same regions (the arm region of the rCMA and the arm region of the cCMA. This study also reported activation of the lateral surface near the locations of activation in anxiety, depression, and OCD provocation. Together, these studies indicate that the *urge to ritualize or itch or move* may be well represented in the CMAs. The functional imaging studies of brain activation during painful stimuli lend further support for this notion. Prominent activations in and around the arm representations of the rostral and caudal cingualte motor areas are the rule, not the exception (e.g., Fig. 28.3 and other work in this volume).

What about surgery for OCD?

A careful analysis of the location of surgeries to treat intractable OCD, as well as chronic pain yields some additional support to the tri-modal theory of OCD that is being developed. When Rauch and Jenike and colleagues (Baer *et al.*, 1995) reviewed their findings of the effects of cingulotomies to treat OCD, they report a success rate of about 30–50%. A close inspection of their lesion sites suggests that these were placed largely adjacent to the arm regions of the posterior rCMA and cCMA. Chiocca and Martuzza (1990) reviewed the worldwide literature on psychosurgery for OCD and concluded that anterior cingulotomy had a success rate of about 50%, anterior capsulotomy or ventromedial tractotomy had a success rate of 50–70%, but combined anterior cingulotomy with a ventromedial or prefrontal leucotomy increased the success rate to 89%. Perhaps the combined surgeries are so successful because they

eliminate both the urge to ritualize and the emotional unpleasantness that is associated with obsessive thoughts about a stimulus. It should be noted, however, that psychological testing reveals very little impairments in these patients. They obviously can still think about objects such as a glove, but the emotional drive and the urge to ritualize have been removed. Somewhat parallel findings have been reported in patients undergoing cingulotomy for intractable pain relief. These patients report that still feeling pain, but the *urge* to do anything about it is alleviated.

What are the contributions of the basal ganglia to OCD?

Consistent metabolic and structural abnormalities have been reported in the putamen and thalamus of subjects with OCD, while somewhat less consistent findings are reported in the caudate and globus pallidus in OCD patients (see Breiter & Rauch 1995). Moreover, during pharmacotherapy for OCD, several regions of the basal ganglia, orbitofrontal, ventromedial frontal, and ACC have been reported to undergo considerable changes in activation. Based upon the foregoing evidence, it is proposed that three distinct basal ganglia loops may be critically affected in OCD (Fig. 28.4). Ideation of obsessive thoughts about objects could involve caudate-SNpr loops with area 12/47 and the lateral **PFC**. Emotional weighting of stimuli may be influenced by SNpr loops with subgenual portions of the ACC. And ritualization could involve GPi loops with the **CMAs**. The degree that a surgery or therapy is successful may depend upon how well it changes the activity in all three circuits, not just one of them.

In further support of this model, it has been observed that GP lesions in humans do not cause obsessions, or emotional changes *per se* (LaPlane *et al*., 1984), but do lead to compulsive behaviors in some cases or 'pure psychic akinesia' that is reversible upon strong external stimulation in other cases. The CMAs receive strong inputs from the pallidal thalamus in the monkey, which may explain the differential effect of GP lesions on the urge to move, but not obsessive ideation or emotional salience. The other two cortical regions (perigenual anterior cingulate and ventrolateral **PFC**) appear to be largely devoid of pallidal input, but receive instead inputs from the SNpr. Thus, pallidal lesions might

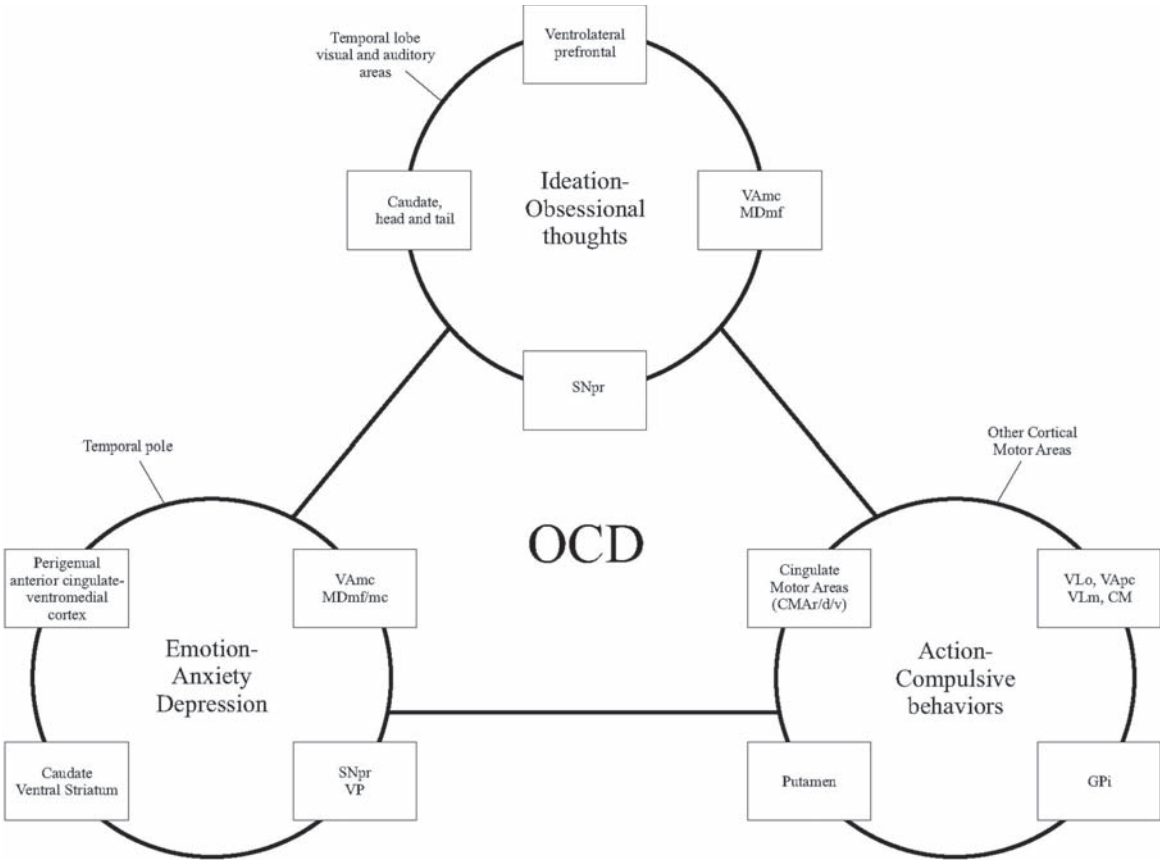

Fig. 28.4 Tri-modal model of OCD produced by alteration of basal ganglia circuitry with prefrontal and cingulate areas.

not be expected to produce obsessions and anxiety symptoms, while SNpr lesions would. Some evidence in support of this was provided by at least two reports of subjects undergoing deep brain stimulation for the treatment of Parkinson's disease (Bejjani *et al.*, 1999; Kulisevsky *et al.*, 2002). In the report by Bejjani *et al.*, when the electrode incorrectly positioned in the SNpr was activated, this subject became emotionally distraught and unequivocally depressed, and this alteration in behavior produced by a single focal activation was association with widespread changes in activity in orbitofrontal and cingulate regions of cortex. These symptoms were completely reversible by turning off the electrode. On the other hand, when the other electrode (that was correctly positioned in the patient's subthalamic nucleus) was stimulated, no emotional changes were reported. A similar type of finding was reported by Kulisevsky *et al.*, except in that report, three subjects all experienced manic episodes with the incorrect electrode stimulation of the subjacent SN.

Relevance of the Open-Loop-OCD Model to Other Psychiatric Disorders

Major depression

As already mentioned, there is considerable evidence for ACC involvement in depressive symptomatology (see Chapter 24 in this volume, and Drevets *et al.*, 1992; George *et al.*, 1992), or provoked anxiety (Gottschalk *et al.*, 1992; Wik *et al.*, 1991). Given the model that is proposed for sACC circuits to be involved in the emotional disturbances of OCD, it is quite possible that a dysfunction of this circuitry could produce dysphoria. These proposals are strengthened by the considerable data showing the role that dopamine can play in promoting euphoria. In addition to the depressive symptomatology, it is also widely recognized that subjects with major depression have significant cognitive impairments. Such disturbances could easily be produced by spreading of the basal ganglia involvement to include circuits that subserve working memory function. Indeed, there may be a parallel situation in OCD and major depression that involves thought fixation (about contaminants or about a poor situation or self image) as well as a strong emotional response produced by the inability to do anything about it. Viewed from this perspective, the major difference between OCD and major depression may simply relate to the compulsive behaviors. It is certainly interesting to note in this regard, that the major drug class used to treat both OCD and major depression is serotonin re-uptake inhibitors, which are highly effective in both conditions.

Attention deficit/hyperactivity disorder

Attention deficit/hyperactivity disorder is a cognitive and behavioral syndrome characterized by deficient attention and problem-solving, along with hyperactivity and difficulty withholding incorrect responses. For the past two decades, there has been considerable research into the neurobiological substrates underlying ADHD, and some of this evidence implicates cingulate—basal ganglia circuitry. For example, among the most consistent findings in volumetric studies of subjects with ADHD are decreases in the size of the caudate and globus pallidus (Singer *et al.*, 1993; Castellanos *et al.*, 1994, 1996, 2003; Aylward *et al.*, 1996; Semrud-Clikeman *et al.*, 2000). Moreover, ADHD subjects have also been reported to display lower glucose metabolism in the premotor and prefrontal cortices, and the thalamus, caudate and cingulate cortex compared with healthy controls (Zametkin *et al.*, 1990), as well as reduced activation in the caudate and cingulate cortex during Go/NoGo or Stroop task performance versus healthy controls (Vaidya *et al.*, 1998; Bush *et al.*, 1999; Rubia *et al.*, 1999). Together with the data already reviewed, these observations suggest that dysregulation of cingulate-basal ganglia circuitry could play a role in the symptomatology of ADHD.

Schizophrenia

Like OCD and ADHD, schizophrenia consists of a set of complex symptoms, and has been associated with changes in the cingulate cortex and the basal ganglia circuitry that subserves it. In schizophrenia, the core symptoms most often include poor cognitive function (impaired working memory and planning), alterations in sensory perception (hallucinations and delusions), flattened affect, and difficulty withholding incorrect responses. The combined symptoms of response inhibition deficits and flattened affect are consistent with the possibility of disruptions in both ACC and MCC circuitry in this disorder. Indeed, alterations in the functional activation patterns of these areas are now well-described in schizophrenic subjects that display attention deficits (e.g., Wang *et al.*, 2005; Morey *et al.*, 2005; Haznedar *et al.*, 2004;), as are changes in basal ganglia structures connected with the ACC and MCC (Galeno *et al.* 2004; Spinks *et al.*, 2005; Buchsbaum *et al.*, 1992; Early *et al.*, 1987).

Cingulate Motor Circuits in the Context of Psychiatric Disorders

The rostral cingulate gyrus is a heterogeneous region of the cerebral cortex that serves as a critical interface for limbic, cognitive, and motor commands. These functions are supported by vast cortical and subcortical networks. At least some components of the subcortical support for the function of the ACC and MCC is provided by multiple basal ganglia circuits with different functional domains. These circuits take the form of either closed-loop circuits that interact predominately with the CMAs in the MCC and open-loop circuits that interact

more prominently with the ACC or other widespread circuits. These circuits have the capacity to support complex motor behavior, the appreciation of emotional state, and perhaps response selection, and planning of actions to achieve desired outcomes. Obsessive-compulsive disorder can be considered as an example of a disorder that could arise from disruption of multiple components of the cingulate-basal ganglia circuitry. On the other hand, less complex disorders (e.g., major depressive disorder) could be considered to be modulated primarily by disruption of a single type of ACC-basal ganglia circuit. Treatments of OCD should therefore be more effective with palliative or restorative therapies of more than one circuit. Future progress in understanding the neurobiology of several other disorders that share some symptomatic overlap with OCD will likely emerge from continued study of the influence of ACC-basal ganglia circuits on behavior.

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