The Basal Ganglia and Cognitive Pattern Generators

by Ann M. Graybiel

Abstract

This article introduces the notion of cognitive pattern generators and suggests, by analogy with the central pattern generators of the motor system, that these pattern generators operate to organize neural activity underlying aspects of action-oriented cognition. It is further proposed that the basal ganglia are involved in the control of cognitive as well as motor pattern generators. Disorders of the basal ganglia may thereby contribute to neural circuit dysfunctions that are expressed as positive and negative symptoms of schizophrenia.


In research on schizophrenia, the basal ganglia have been relatively neglected, undoubtedly because schizophrenia centrally involves disordered cognition and thought, functions attributed to the cerebral cortex. The pharmacology of schizophrenia, inferred from early treatment with dopamine receptor antagonists and more recent treatment with clozapine, nevertheless has placed the basal ganglia among the candidate forebrain regions implicated in the etiology of schizophrenia (Anden 1972; Suterlbow and Koob 1987; Carlsson 1988; Carlsson and Carlsson 1990; Meltzer 1991; Gingrich and Caron 1993; Carpenter and Buchanan 1994). The dopamine systems most often put forth as being involved are the mesolimbic and mesocortical systems (Stevens 1973; Grace 1991; Seeman 1993). However, some evidence has suggested that the nigrostriatal dopamine system and its striatal targets (the caudate nucleus and putamen) may also be implicated in the etiology of schizophrenia (Mettler 1955; Klawans et al. 1975; Early et al. 1987; Suterlbow and Koob 1987; Lidsky et al. 1979; Buchsbaum 1990; Robbins 1990; Jernigan et al. 1991; Buchsbaum et al. 1992a, 1992b; Buchanan et al. 1993; Gingrich and Caron 1993; Heckers et al. 1993; Miller and Chouinard 1993; Siegel et al. 1993; Carpenter and Buchanan 1994; Elkashef et al. 1994; Holt et al. 1994, and submitted for publication; Hokama et al. 1995; Holcomb et al. 1996; Roberts et al. 1996).

In this article, I consider two reasons why the basal ganglia should be highlighted as potentially important in the pathophysiology of schizophrenia. First, I suggest that schizophrenia should be considered as a circuit disease—not a disease attributable to pathology in one brain site; for example, the thalamus or the anterior cingulate gyrus, temporal cortex, or dorsolateral prefrontal cortex (Weinberger 1987; Weinberger et al. 1992; Bogerts 1993; Andreasen et al. 1994; Dolan et al. 1995; Silbersweig et al. 1995). Within this framework it seems likely that the basal ganglia are centrally implicated in neural circuits that are dysfunctional in individuals with schizophrenia. The second reason to focus on the basal ganglia derives from the cardinal symptoms associated with schizophrenia (Carpenter and Buchanan 1994). The negative or residual symptoms of schizophrenia include extreme apathy, evidenced in the motor as well as in cognitive and affective spheres. The positive symptoms of schizophrenia include disorganization of thinking and planning, behavioral stereotypies, and loss of ability to distinguish between real and imagined events as exemplified by hallucinations and delusions. These behavioral characteristics fit well with the idea that the basal ganglia may be critically involved in the control of cognitive pattern generators as well as motor pattern generators.

The Basal Ganglia and Goal-Directed Behaviors

Most current thinking about the basal ganglia divides these structures into two parallel systems: (1) the dorsal striatal-dorsal pallidal system, including the caudate nucleus, the putamen, and the globus pallidus, and (2) the...
The Basal Ganglia and Action Planning

In the motor field, the basal ganglia are also thought of as part of the “planner mechanism” that drives pattern generators, but these are the central motor pattern generators of the spinal cord and brainstem (figure 2) (see Rossignol and Dubuc 1994 for review). Important literature is accumulating on participation of the basal ganglia in the development of and expression of sequential motor acts (figure 3) (see Graybiel 1995 for review). In the macaque monkey, neurons in the caudate nucleus and putamen have been shown to fire selectively in relation to particular learned motor sequences (Kermadi and Joseph 1995; Strick et al. 1995), as do units in the globus pallidus (Strick et al. 1995). Such sequence-specific neural firing is a hallmark of the supplementary motor area (SMA) and the pre-SMA, regions of the cortex that are targets of basal ganglia outflow (Tanji 1994). In primates, including humans, these cortical areas are thought to be involved in

Figure 1. Functional diagram of neural circuits underlying goal-directed behavior

Figure 2. Functional view of basal ganglia as parts of neural circuits underlying motor planning
Figure 3. Basal ganglia circuits contributing to adaptive control of action

Diagram of some neural circuits that may be involved in learning behavioral routines (left) and expressing them after learning (right). The striatum is shown near the center of the diagram. Note that the limbic system and prefrontal cortex provide inputs that may be involved in biological evaluation and memory-contingent evaluation. The substantia nigra pars compacta (SNC) may provide input related to reward. Together, these circuits are considered to be parts of the cognitive pattern generator circuits shown in figure 4. More posterior parts of the cortex as well as the thalamus, send inputs that may encode segments of action plans being generated in the cortex and affiliated thalamic nuclei. The striatum and the pallidum are envisioned as helping in the selection of action components and in the activation of programs for action that are sent either to the brainstem and spinal cord pattern generator mechanisms or to the action-oriented cognitive pattern generators of the cerebral cortex and associated circuits. Note that the large number of loop systems in basal ganglia circuitry, only some of which are shown. GPe = globus pallidus, external segment; GPi = globus pallidus, internal segment; SNr = substantia nigra, pars reticulata; Sth N = subthalamic nucleus. (Modified from Graybiel 1995.)

the motor planning that occurs before motor acts. For example, in the monkey there are units in the SMA that fire in relation to a sequence of highly learned motor acts (Tanji and Shima 1994; Tanji et al. 1995; Shima et al. 1996). In the human, the supplementary motor area and nearby regions have been shown to be active in subjects thinking about but not actually making movements (Ingvar and Philipson 1977; Deecke 1987; Roland 1987; Tanji 1994; see Brooks 1995 for further review).

The results of positron emission tomography studies carried out to compare the activation patterns induced by free, nonsequential movements with those of learned sequential movements suggest that the striatum as well as the SMA and related frontal cortical regions are differentially activated in relation to the acquisition and expression of learned complex movements (Seitz and Roland 1992; Jenkins et al. 1994; see Tanji 1994 and Graybiel 1995 for review). Finally, electrophysiological evidence suggests that, as a monkey learns a new sensorimotor behavior through reward-based conditioning, there are systematic changes in the responsiveness of neurons in the caudate nucleus and putamen (Aosaki et al. 1994; Graybiel et al. 1994).

These experiments suggest that the dorsal basal ganglia (the “basal ganglia” in the motor field) either are part of the motor planner itself or are in a loop with the motor planner (figure 2). These structures also have the potential to activate drive-specific behavioral pattern generators related to innate behavior. For example, in rodents, a relatively restricted part of the caudoputamen is essential for the execution of highly patterned grooming responses that are thought to be instinctual (Berridge and Whishaw 1992). A nearby but different region of the caudoputamen has been identified as necessary for the oral stereotypes induced by amphetamine (Dickson et al. 1994).

Cortico-Basal Ganglia and Thalamo-Basal Ganglia Loops

Implicit in this discussion so far is the notion that the basal ganglia cooperate with the executive planning regions of the forebrain in driving specific behavioral repertoires such as fixed action patterns through central pattern generators and, more generally, in sculpting pattern generator activity to bring about coordinated movements appropriate to particular behavioral contexts. These functions seem far removed from the issue of cognition and its control or dysfunction. Several characteristics suggest, however, that at the circuit level the basal ganglia are associated intimately with brain structures thought to be involved in cognitive processing (for review, see Graybiel 1995; Houk 1995; Kimura and Graybiel 1995; Parent and Hazrati 1995a, 1995b).

The first and outstanding characteristic is that the outflow from the basal ganglia is preferentially directed toward the frontal lobes. Together, the striatopallidal system and the striatonigral system projecting to the pars reticulata of the substantia nigra have access, via the thalamus, to a large part of the frontal cortex in primates. Moreover, this frontal projection system is by far the most massive ascending system of the basal ganglia.

Second, the basal ganglia receive their most massive inputs from forebrain regions. These regions include nearly all, if not all, of the neocortex, the centre median-parafascicular (CM-Pf) complex and the midline nuclei of the thalamus, and the basolateral amygdaloid complex. Moreover, among the cortical inputs, those from the frontal and parietotemporal association are the most massive.

Third, the basal ganglia are a principal target of central state-control projection systems arising from amine-
gic brainstem cell groups. These systems include not only the dopamine-containing nigral-ventral tegmental-retrorubral complex but also certain of the serotonergic raphe nuclei and (for the ventral striatum) the noradrenergic locus coeruleus.

Fourth, the basal ganglia have direct access to the nucleus reticularis of the thalamus. This nucleus is thought to exert control over the state of thalamocortical transmission (Steriade 1993; Groenewegen and Berendse 1991).

Taken together, these characteristics suggest that the basal ganglia (1) operate in conjunction with the cerebral cortex and thalamus in forebrain neural processing at the highest levels, and (2) are in a position to influence the activity states of such forebrain systems.

Are these characteristics uniquely human, as some might require for evidence that the basal ganglia could be involved in the etiology of schizophrenia? Almost certainly not. For example, tract tracing evidence has shown that even in birds there is a highly differentiated input to the striatum from forebrain regions thought to be homologous to cerebral cortex (Veenman et al. 1995). On the other hand, the striatum is thought to have expanded markedly during evolution. The association cortex that most strongly projects to the striatum, the reciprocally interconnected CM-Pf complex of the thalamus, and the frontal cortical targets of basal ganglia outflow also assume their largest size in the primate brain and especially in the human brain. The functions of cortico-basal ganglia interactions thus appear to have been elaborated, not reduced, in species with complex cognitive capacities.

Cognitive Pattern Generators

The picture that emerges from the known physiology and anatomy of the basal ganglia is that these structures have neural targets of at least four types: (1) premotor cell groups of the brainstem, (2) motor and premotor-SMAs of the cortex, (3) prefrontal association cortex and some temporal association cortex, and (4) cell groups associated with forebrain state control.

A further characteristic of the basal ganglia is that they are involved in loop circuits (Graybiel and Ragsdale 1979; Parent and Hazrati 1995a, 1995b). For the cortex, these circuits have been divided into sets of parallel loops (Graybiel 1984; Alexander et al. 1986). But these are not the only such circuits. The CM-Pf complex, the subthalamic nucleus, the substantia nigra, and the brainstem pedunculopontine nucleus all are in loop circuits with the basal ganglia.

These dominant patterns of connectivity suggest that iterative patterns of activity could be set up in basal ganglia loop circuits and their affiliated structures and that, as a consequence, these basal ganglia circuits could be used for establishing and later expressing behavioral repertoires built up through experience. For the motor functions of the basal ganglia, this notion is supported by evidence that the basal ganglia are involved in the control of brainstem pattern generators and of frontal cortical areas implicated in motor planning, as discussed above.

For cognitive functions, there may also be cognitive pattern generators, analogs of the central pattern generators we are familiar with in the motor sphere. I further propose that the basal ganglia may be involved with the development and execution of action-oriented cognitive patterns by way of these cognitive pattern generators (figure 4). The patterns generated are organized in relation to future action. They are not expressed physically in motions of the body, but rather are expressed cognitively. According to this view, activity-dependent, repetitive patterns may be set up not only in the motor system but also in brain regions subserving cognitive activity. With repetition, dominant modes of activation of these circuits may emerge. It seems highly likely that the loop circuits that link the basal ganglia and frontal cortex influence the acquisition, retention, and expression of such cognitive patterns (figure 4).

Figure 4. Functional view of neural circuits modulating action-oriented cognitive activity and motor activity

Cognitive Activity

- Cognitive Pattern Generators
- Evaluation
- Memory
- Sensory-motor Stimuli

Motor Activity

- Motor Pattern Generators
- Dopamine
- Serotonin

Schematic diagram summarizing hypothesis discussed in text that, in addition to motor pattern generator in the hindbrain, there are cognitive pattern generators in the forebrain. The basal ganglia are shown as influencing both.
What would be the nature of such action-oriented cognitive patterns? The phrase, "a habit of thought," catches at least one aspect of what is meant here. In the motor sphere, the basal ganglia and frontal cortex are thought to be involved in the building up of sequential motor behaviors from movement elements, with motivational tone as a key reinforcer. These functions underlie the notion of the basal ganglia's involvement in habit learning (Hirsh 1974; Mishkin and Petrie 1984; Graybiel 1995; Knowlton et al. 1996). What I propose is that a comparable building up of cognitive patterns from simpler cognitive elements may occur, and this process may result from activity-dependent engagement of corticobasal ganglia loops.

**Basal Ganglia and Cognitive Action Plans.** The evidence reviewed so far suggests that the basal ganglia have a unique dual relationship to motor and motivational circuits in the forebrain and brainstem. Is this dual relationship really simply a reflection, in functional terms, of the division of the basal ganglia into ventral (motivational) and dorsal (motor) parts? Several types of evidence suggest not. First, the motivational (ventral part) is itself interlinked with the hippocampal system in which cognitive maps and declarative memory functions are built up (O'Keefe and Nadel 1978; Zola-Morgan and Squire 1993). Second, the ventral system may be a key executive system by which the hippocampus engages the motor system. There is, in fact, good evidence that the heightened locomotor activity that is provoked by psychomotor stimulant drugs depends on the ventral striatum (Robinson and Becker 1986; Kalivas and Stewart 1991).

Nor is the dorsal striatum strictly a "motor" structure. First, a large part of the caudate nucleus and parts of the anterior putamen receive inputs primarily from association cortex quite distinct from the motor and premotor areas of the frontal lobes (Parent and Hazrati 1995a), and the caudate nucleus has been implicated in nonmotor symptoms of extrapyramidal motor disorders (Bhatia and Marsden 1994). Moreover, there are two prominent neurochemically defined tissue compartments in the striatum—striosomes and matrix (Graybiel and Ragsdale 1978)—and the input-output connectivity of these two compartments suggests that striosomes, which are particularly well developed in the caudate nucleus, have a special affiliation with the limbic system. For example, the striosomal system of the caudate nucleus receives limbic-related inputs from the orbital and anterior cingulate cortex and from the amygdala (Eblen and Graybiel 1995 and references therein). Because the striosomes lie embedded in surrounding matrix tissue that has clear connections with sensorimotor brain systems, striosomes may provide local links, especially in the caudate nucleus and anterior putamen, for limbic and motor processing (Eblen and Graybiel 1995; see figure 5).

In monkeys, striosome-matrix borders contain concentrations of neurons whose activity changes on the basis of reward during sensorimotor conditioning (Aosaki et al. 1995). In rats, striosomes have been shown to be preferred sites for intracranial self-stimulation (White and Hiroi 1995). They have also been shown to project to the pallidal region that, in turn, projects to the lateral habenula, a structure also implicated in limbic reward circuits (see Ellison 1994). Particularly interesting is the fact that striosomes appear to project to the dopamine-containing substantia nigra pars compacta itself, which contains neurons that in monkeys fire in relation to primary rewards or to symbols of these rewards (Schultz et al. 1993). This feature raises the possibility that limbic-related striosomes might influence fundamental mechanisms involved in the development of action plans based on reward (Eblen and Graybiel 1995; Graybiel and Kimura 1995; Houk et al. 1995).

The striosome-matrix compartmentalization of the striatum is not the only way for interactions between limbic and sensorimotor information in basal ganglia circuits.
to occur. In the rat, direct connectivity between the dorsal and ventral systems has been demonstrated anatomically at the level of basal ganglia output nuclei (Bevan et al. 1995). Thus, there are likely to be multiple, and functionally specific, motivation-related subcircuits within even the dorsal striatum and dorsal pallidum.

The widespread interactions of individual basal ganglia circuits suggest that they are part of a distributed neural mechanism that influences action plans according to information from a large number of forebrain regions. In primates, much of the caudate nucleus is embedded in cortico-basal ganglia loops that link it with the prefrontal cortex, including the association cortex, that are thought to participate not in motor control per se, but in high-level cognitive control of action (Fuster 1989). Thus, although the motor sectors of the dorsal striatum and dorsal pallidum appear to be predominantly related to skeletomotor function, this may not be true for much of the remainder of the striatopallidal system. These less strictly motoric basal ganglia loops may, functionally, be part of cognitive planning mechanisms in the forebrain, many of which ultimately are designed to help control behavioral action.

The Basal Ganglia and Building an Identity. The link between intent and action may also have a quite specific function during development. This set of circuits may provide part of the neural mechanism for building up cognitive patterns involving recognition of the self. It is well documented that, as voluntary motor behaviors develop and as feedback about the consequences of these behaviors occurs, the perceptuomotor world of the infant develops (Gibson 1969). These same correlations among intent, action, and consequence also offer a simple way for the young organism to acquire the distinction between actively initiated and passively received events. As a result, the infant can acquire the recognition of self as actor. The iterative nature of many basal ganglia connections and the apparent involvement of the basal ganglia in some forms of learning could provide a mechanism for this development of self-awareness.

The Basal Ganglia and Reality Testing. A similar monitoring of feed-forward commands related to action planning and feedback information about the consequences of such actions ultimately must influence the child’s evolving concept of external reality. The child makes hypotheses about the world, checks perceptual data, evaluates, and adjusts behavior around it. The child’s common attribution of actor roles to inanimate objects across a range of experiences suggests how deeply ingrained this characteristic behavior may be.

The neural activity related to such cognitive acts may not primarily involve the basal ganglia. It is known, for example, that association connections linking different cortical areas arise mainly from neurons that do not project to the basal ganglia. However, as the organism acts with intent and evaluates the consequences, circuits involving the basal ganglia and frontal cortex almost certainly become activated. It has been argued elsewhere that one of the functions of the striatum, in particular, may be to mediate binding in the motor system (Graybiel et al. 1994). This view is based on evidence that temporally coordinated firing patterns can be set up in widespread regions of the striatum as a result of sensorimotor learning. Such coordinated firing could help align the activity in different motor circuits temporally so as to produce coordinated motor acts.

For the more anterior parts of the striatum, a similar binding function may hold for cortico-basal ganglia circuits involved in mediating cognitive activity. Thinking, planning, organizing perceptuomotor information, loading or tapping memory systems, and other cognitive operations depend just as critically on spatiotemporal coordination as does sensorimotor processing. Such cognitive brain activities, insofar as they involve the frontal cortex, should at least in part be influenced by activity in the caudate nucleus. Such synchronizing or binding of frontostriatal circuits may be important in the self–other interplay on which the notion of external reality is first based, whether the interaction is with other organisms or with objects.

Interestingly, the striatal mechanisms found to undergo temporal coordination during sensorimotor learning in the monkey have properties suggesting that they are striatal interneurons, and, further, that they may be the cholinergic interneurons of the striatum (Graybiel et al. 1994; Aosaki et al. 1995). Evidence from study of postmortem brains of patients diagnosed as having schizophrenia suggests that striatal interneurons may be abnormal in these brains and that cholinergic neurons, in particular, may be affected (Heckers et al. 1993; Holt et al. 1994, and submitted for publication). There is also evidence that in brains from schizophrenia subjects the spines of striatal projection neurons are reduced in size (Roberts et al. 1996). As these spines are the main targets of the massive cortical projection to the striatum, coherent patterns of striatal activation could also be disturbed (Parthasarathy et al. 1992; Cowan and Wilson 1994; Graybiel et al. 1994). This again suggests that one core defect in schizophrenia may be related to timing dysfunctions in cortico-basal ganglia circuits.

The Basal Ganglia and Symptoms of Schizophrenia

This article has suggested that the basal ganglia are forebrain structures involved in goal-directed behavior, in
learning related to motor and cognitive action plans, and in action planning itself or its neuromodulation. It is further suggested that during development, the basal ganglia may function in the monitoring of intention and its consequences and actions and, as a result, participate in the development of motor and cognitive patterns that differentiate self from others. If we consider the basal ganglia as integral parts of forebrain circuits involved in these functions, it is perhaps not too far-fetched to think that disruption of these basal ganglia circuits could contribute to both the negative and the positive symptoms of the disorder. Motivated, goal-directed behaviors could be disabled, and planning, ordered action repertoires, and recognition of self versus other disrupted.

This argument is perhaps most easily made for the negative symptoms of schizophrenia. The major clinical symptom resulting from lesions of the caudate nucleus in the human is abulia, a lack of initiative and drive (Bhatia and Marsden 1994). There is more than a superficial resemblance between this state and the negative symptoms of schizophrenia, in which apathy, loss of motivation, and disruption of goal-directed behaviors are manifest. Indeed, the extreme of this continuum, catatonia, is expressed as a motor disorder.

For the positive symptoms of schizophrenia, the distance from classical ideas about the basal ganglia is greater. But when the basal ganglia are viewed as parts of loop circuits, and when schizophrenia is viewed as a circuit disease, this distance diminishes. Motor stereotypes and disordered cognitive planning can be seen as reflecting dysfunctions of cortico-basal ganglia circuits that link the basal ganglia with the frontal and medial cortex, including the anterior cingulate cortex. Disorders in attention can be viewed as implicating basal ganglia loops with the thalamic reticular and intralaminar nuclei, the cingulate cortex, and the aminergic cell groups of the brainstem. Inability to sort out real from hallucinatory experiences may in part reflect disordering of the iterative loops needed to evaluate the consequences of self-initiated versus other-initiated actions. Intrusions of unintended mental experiences could be interpreted as "other" by this argument. Finally, disordered timing in local circuits in the striatum (Graybiel et al. 1994) or in neural loops typifying basal ganglia circuitry (Graybiel 1984) could contribute to the abnormal cognitive experiences. Such symptoms, expressed in the cognitive sphere, bear many similarities to the motor signs of basal ganglia disorders. The similarities suggest that common neural mechanisms may coordinate physical and cognitive action.

References


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