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Review

The basal ganglia: An overview of circuits and function

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Abstract

The technique of electrical stimulation of brain tissue—known clinically as deep brain stimulation (DBS)—is at the fore of treatment of human neurological disease. Here we provide a general overview highlighting the anatomy and circuitry of the basal ganglia (BG). We introduce common disease states associated with BG dysfunction and current hypotheses of BG function. Throughout this introductory review we direct the reader to other reviews in this special issue of Neuroscience and Biobehavioral Reviews highlighting the interaction between basic science and clinical investigation to more fully understand the BG in both health and disease.

Keywords: Movement disorders; Dopamine; Cognition; Obsessive-compulsive disorder; Striatum

Contents

1. Introduction

The technique of electrical stimulation of brain tissue—known clinically as deep brain stimulation (DBS)—is at the fore of treatment of human neurological disease. Remarkably, it improves quality of life for patients suffering from movement disorders such as Parkinson's disease and essential tremor. It provides relief to patients suffering from chronic pain and recently, it is meeting with success in the treatment of psychiatric illness such as chronic depression and obsessive-compulsive disorder. The possibilities for the technique of electrical stimulation of the brain appear boundless. For example, stimulation of brain

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regions involved in feelings of hunger and satiety may prove a comparatively safe and effective method of treatment for morbid obesity (Covalin et al., 2005). If electrical stimulation can protect the brain from further degeneration as some data suggest, DBS may even hold promise for treating currently intractable and ultimately fatal neurodegenerative diseases, such as Huntington's disease.

Electrical stimulation of the brain is one of the oldest and most well-studied techniques used to explore brain function. Since its introduction into the laboratory and neurosurgical theatre over 150 years ago, our understanding of the neuronal control of voluntary movement, sensation, cognition and even emotion has increased. The use of electrical stimulation to treat basal ganglia (BG) disorders began when Benabid, instead of using electrical current to create a lesion, observed that high frequency stimulation could ameliorate motor symptoms of Parkinson's disease, eliminating the need to permanently damage brain tissue. DBS is an example of how clinical application and scientific investigation involving laboratory animals can work hand in hand. The use of DBS clinically is revealing mechanisms of action of electrical stimulation of neural tissue. In particular, DBS used for the treatment of movement disorders combined with laboratory experiments using electrical stimulation continue to reveal new aspects of BG function and the role this massive group of forebrain structures plays in behavior. For these reasons, this special issue of *Neuroscience and Biobehavioral Reviews* is dedicated to the topic of DBS. The focus of this issue is on the contribution of electrical stimulation techniques both in the laboratory and in the clinic. From a basic science perspective, our hope is that this issue will help further the scientific community's understanding of the role of the BG in movement, cognition and even emotion. From a clinical perspective, we also hope to further our understanding of the DBS technique as well as the healthy and pathological BG in order to optimize DBS as a treatment for human neurological disease.

In the introductory review that follows, we provide a general overview of the structures making up the BG and we briefly review the anatomical circuitry linking these structures. We then describe five neurological conditions resulting from BG malfunction. Finally, we describe three conceptual models that have been proposed to explain how BG dysfunction produces disease symptoms. This overview provides a general background to support the content of the subsequent papers of this issue.

2. BG anatomy and circuitry

2.1. BG influence many neural systems

There are several nuclei comprising the BG. Most project exclusively to other nuclei within the BG, creating a large subcortical network within the forebrain. The two output nuclei of the BG are the globus pallidus internal segment (GPi) and the substantia nigra pars reticulata (SNr) whereas the main input nucleus is the striatum (caudate and putamen collectively). The subthalamic nucleus (STN) can also be considered an input nucleus because, like the striatum, the STN receives direct input from the cerebral cortex (Kitai, 1981; Nambu et al., 2002). Through the two output nuclei, the BG innervate only three structures, the thalamus, the superior colliculus, and the pedunculopontine nucleus (PPN). Although, its influence is mediated through only three target structures, BG influence is far reaching. Through the thalamic target, the BG influence motor, sensory, and cognitive cortical information processing (Hoover and Strick, 1999; Middleton and Strick, 1994, 1996, 2002). Through the superior colliculus target, the BG influence movements of the head and eyes (Hikosaka et al., 2000). Through the PPN target, the BG influence spinal cord processing and aspects of locomotion (Garcia-Rill et al., 1983) and postural control (Takakusaki et al., 2003). Indeed, recent studies show that DBS of PPN can be used to treat the postural instability seen in Parkinson's disease (Mazzone et al., 2005; Plaha and Gill, 2005). In contrast to the small number of output targets of BG, the inputs to the BG arise from virtually the entire cerebral cortex. Thus, the BG are well-poised to have far reaching influence on many neuronal pathways and information processing systems. It is because of this that the role of the BG has remained so elusive for so long. The varied cortical inputs and broad influence on other neural structures is also the likely reason why BG disease produces such varied and complex symptoms.

2.2. The striatum, globus pallidus, STN and substania nigra are the major BG nuclei

An overview of the anatomical structures and general circuitry making up the BG is provided (Fig. 1). We first discuss the inputs to the BG and then discuss the outputs. We conclude this section with a brief description of arguably the most important neuromodulatory system of the BG, the dopaminergic system.

2.2.1. The striatum

The striatum, the major input structure of the BG, is comprised of two, functionally similar nuclei, the caudate and putamen. At the rostral end of the striatum, the two nuclei appear as one large structure. Further caudally, the caudate and putamen are separated by the internal capsule. The striatum receives excitatory input from many cortical areas (Kemp and Powell, 1970) and thalamic nuclei (Smith et al., 2004). Anatomical and physiological studies have shown that different cortical areas project to distinct regions of the caudate and putamen. As a result of this cortical-BG anatomy, five parallel information processing circuits can be identified; a motor circuit, an oculomotor circuit, a dorsolateral prefrontal circuit, a lateral orbitofrontal circuit, and an anterior cingulate circuit (Alexander et al., 1986). These anatomically distinct circuits are

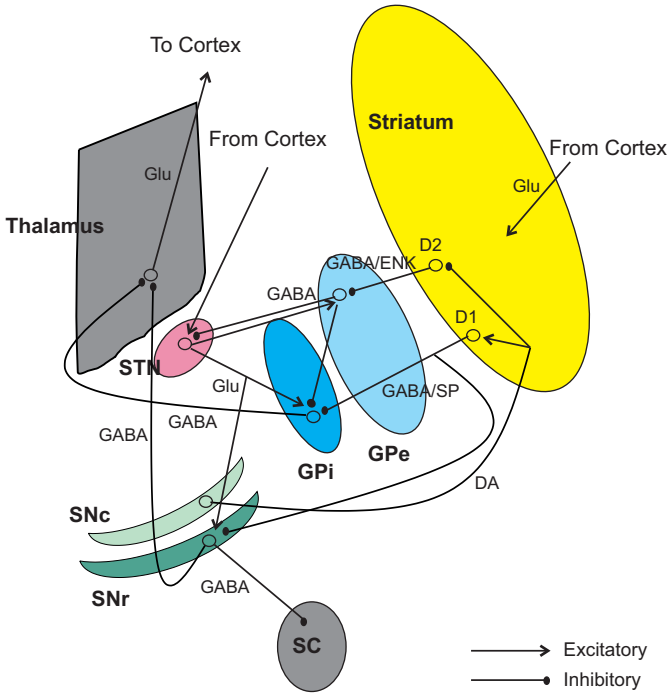

Fig. 1. Schematic diagram of BG circuitry. BG target structures are shown in gray. Abbreviations: GPe, globus pallidus external segment; GPi, globus pallidus internal segment; SC, superior colliculus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; DA, dopamine; D1, dopamine D1 receptor subtype; D2, dopamine D2 receptor subtype; Glu, glutamate; ENK, enkephalin; SP, substance P.

considered partially closed in that some, but not all, of the cortical regions providing the input are also the targets of the outputs. For example, in the motor circuit, the cortical afferents to the BG arise from primary motor cortex, somatosensory cortex, premotor cortex and supplementary motor cortex. The primary target of the BG motor circuit through the thalamus is the supplementary motor cortex. Whether these five circuits are completely segregated or overlapping, remains an important question for investigation (Cui et al., 2003; Parthasarathy et al., 1992; Selemon and Goldman-Rakic, 1985). Two of the five circuits, the motor and oculomotor, have names related to their function because there is a considerable amount of knowledge on the function of these two circuits compared to the other three. Ongoing experimental investigations focus on the roles of the cortical regions making up the three other circuits involved in cognition, emotion and motivation. Whether or not individual circuits will turn out to have exclusive roles in these processes remains for future work. Fig. 2 provides a schematic of the regional organization of cortical inputs to the striatum. Based on anatomical and electrophysiological findings, BG can be divided roughly into three territories, a sensorimotor, an associative or cognitive and a limbic region (Parent and Hazrati, 1993, 1995a).

The striatum also receives a major input from dopaminergic neurons located in the ventral midbrain. Dopaminergic innervation of the striatum arises from two nuclei, the substantia nigra pars compacta (SNc) and the ventral tegmental area (VTA). The dopamine (DA) arising from the VTA innervates the caudate, putamen, and the ventral striatum (also called the nucleus accumbens). Much evidence implicates the mesolimbic DA system in mechanisms of reward and addiction (Kelley, 2004; Schultz, 1998, 1999, 2002). A third DA system arises in the hypothalamus.

There are two types of DA receptors, D1 and D2, on striatal projection neurons (also known as medium spiny projection neurons). Both the D1 and D2 DA receptors are G-protein coupled receptors. When DA is bound to the D1 receptor, a second messenger-signaling cascade is initiated, resulting in depolarization of the neuron. When DA is bound to D2 receptors, in contrast, a second messenger cascade resulting in neuronal hyperpolarization occurs

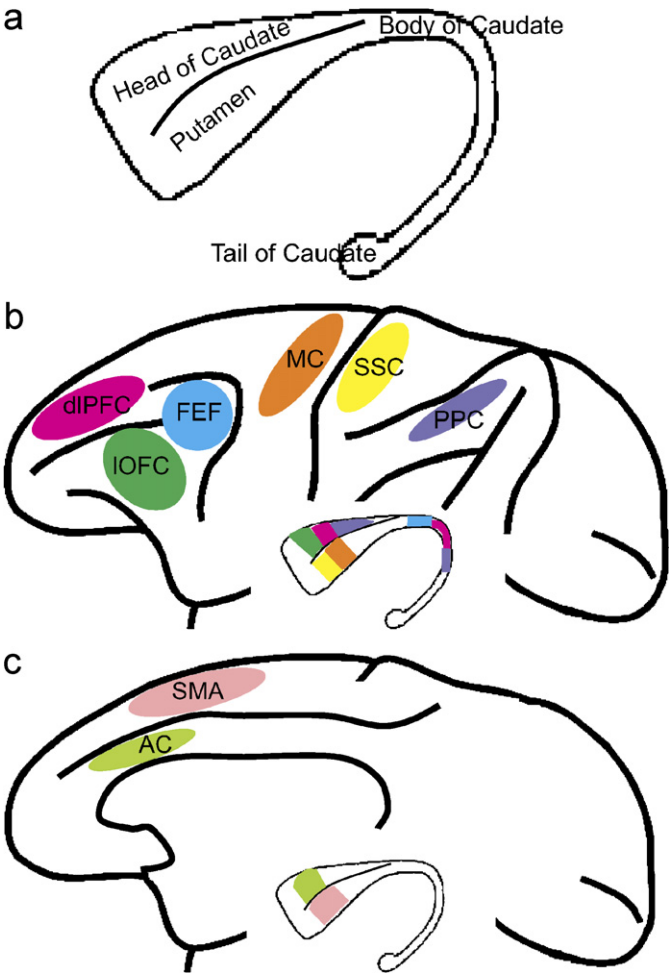

Fig. 2. Schematic showing anatomy of the striatum (a). Representative lateral (b) and medial (c) illustrations of cortical areas and their connections to the striatum. The colored segment in the striatum represents the area of the striatum receiving projections from the cortical area of the same color. Abbreviations: AC, anterior cingulate cortex; dlPFC, dorsal lateral prefrontal cortex; FEF, frontal eye field; lOFC, lateral orbitofrontal cortex; MC, motor cortex; PPC, posterior parietal cortex; SMA, supplementary motor area; SSC, somatosensory cortex. Compiled from Alexander et al. (1986).

(reviewed in Sealfon and Olanow, 2000). Thus, the action of D1 receptors is to enhance cortical-striatal influence whereas the action of D2 receptors is to reduce cortico-striatal influence. However, because D1 and D2 receptor agonists may act synergistically to treat parkinsonian symptoms, it is likely to be more complicated than this (Jenner, 2003). Evidence suggests that there is a differential distribution of DA receptor subtypes on the dendrites of striatal neurons. Those striatal neurons projecting directly to the output nuclei of the BG have D1 receptors whereas those striatal neurons projecting indirectly, through other BG nuclei to the output nuclei, have D2 receptors on their dendrites. This dichotomy led to the classic notion of the indirect pathway inhibiting movement and the direct pathway facilitating movement (Gerfen et al., 1990). Although recent evidence showing co-localization of DA receptors on striatal neurons calls this into question (Aizman et al., 2000). Nevertheless, the importance of DA for information transmission at the cortical-striatal synapse is incontrovertible.

In addition to the projection neurons of the striatum, there are many types of interneurons within the striatum. The three classifications of striatal interneurons are the cholinergic large aspiny neuron (Bolam et al., 1984; Kemp and Powell, 1971), also known as tonically active neurons (TANs) because of their physiological phenotype, the parvalbumin/GABAergic medium aspiny neuron, (Kemp and Powell, 1971; Kita and Kitai, 1988) and the somatostatin, neuropeptide Y, and NADPH diaphorase containing aspiny neurons (Gerfen and Wilson, 1996). Compared to the other striatal interneurons, the relationship of TANs to behavior is the most well-studied (Pisani et al., 2001; Yamada et al., 2004). There has been much focus on the importance of DA as the main neuromodulator in the BG and we believe an exciting future direction for research will be to understand more fully the functional implications of the microcircuitry of input from cortex, thalamus, and interneurons to the medium spiny projection neurons of the striatum as well as the role of non-dopaminergic neuromodulation (Smith et al., 2004).

2.2.2. *Globus pallidus*

Like the striatum, the globus pallidus (GP) is separated into two nuclei, in this case, by small fibers of passage and pallidal border cells. The more laterally positioned nucleus is called the globus pallidus external division (GPe) whereas the medially positioned nucleus is called the globus pallidus internal segment (GPi—often referred to as the entopeduncular nucleus in rodents). Both segments of GP receive GABAergic input from the striatal medium spiny projection neurons, but this projection originates from different classes of medium spiny neurons. The direct, striatal–GPi pathway arises from GABA/substance P containing medium spiny neurons whereas the indirect, striatal–GPe–STN–GPi pathway arises from the GABA/enkephalin containing medium spiny neurons (Gerfen and Wilson, 1996). The dichotomy between the direct and indirect pathways plays an important role in models of BG function described below. However, anatomical evidence points out that the intrinsic circuitry is far more complex than the current models. For example, single axons of striatal neurons terminate in all nuclei, GPe, GPi and SNr (Parent and Hazrati, 1995a) demonstrating that the direct and indirect pathway is at the very least, an oversimplification. Moreover, anatomical evidence reveals a direct projection from the GPe to the GPi (Parent and Hazrati, 1995b) rather than through the STN, even further precluding a simple direct and indirect pathway dichotomy. A complete understanding of BG function will undoubtedly have to incorporate these anatomical connections.

2.2.3. *STN*

The STN lies just ventral to the thalamus. Traditionally, the anatomical position of the STN in the BG is within the indirect pathway. The STN receives afferents from the GPe. STN has reciprocal projections to GPe and also projects to the GPi and the SNr. The projections from STN are the only excitatory projections within the BG (Kitai and Deniau, 1981). In light of anatomical studies, it is clear that the STN can also be considered an input nucleus since it receives direct input from the cerebral cortex (Hartmann-von Monakow et al., 1978; Kitai and Deniau, 1981; Nambu et al., 2002). How the cortical–STN pathway fits in models of BG function beyond its position within the indirect pathway, is unclear. Our understanding of the role of BG in health and disease will benefit greatly from basic science experiments designed to test models of the cortico-STN pathway in behavior in humans and other animals.

2.2.4. *Substantia nigra*

The substantia nigra is comprised of a compact and a diffuse clustering of neurons. Both clusters lie dorsal to the cerebral peduncle in the ventral midbrain. The SNc contains large DA cells that provide the dopaminergic input to the striatum also referred to as the nigro-striatal DA system. There are also reciprocal connections from the striatum to the SNc, but the functional significance of this connection is not clearly understood. The substantia nigra pars reticulata (SNr) is distinct from the SNc. Neurons in SNr contain GABA (Chevalier et al., 1981a, b) and along with the GPi, the SNr is an output nuclei of the BG. Also like GPi, SNr receives inhibitory input from the striatum through the direct and indirect pathways. The relationship of the SNr to eye movements has been studied extensively. The work in non-human primates and rodents has contributed the bulk of what we know about the importance of disinhibition for the generation of voluntary movement (Chevalier and Deniau, 1990; Chevalier et al., 1981b, 1984; Hikosaka and Wurtz, 1989). For example, prior to a rapid saccadic eye movement SNr neurons display a pause in activity, while superior colliculus neurons show a burst in activity. Current conceptual models of the BG control of eye movements, for which there is considerable support (Hikosaka et al., 2000)

suggest that the pause in the SNr provides a transient disinhibition of the superior colliculus. The pause in SNr activity is correlated with an increased discharge of superior colliculus neurons leading to an eye movement command. From more recent work, it is becoming clear that the SNr is involved in cognitive processes in addition to its role in movement (Basso and Wurtz, 2002; Bayer et al., 2002; Hikosaka and Wurtz, 1983; Wichmann and Kliem, 2004). Understanding exactly the role of the SNr in cognitive processes leading up to movements will be an important direction for future research. Indeed, cognitive side effects that are sometimes reported in patients with DBS (Deuschl et al., 2006) may result from current spread into the SNr. Understanding the SNr better may lead to more precise DBS methods to minimize these unwanted side-effects.

Our knowledge of BG anatomy is considerable, but by no means complete. As the field of BG research advances it will be critical to not only form a more complete picture of the anatomical projections of the BG, but also to understand the function of those projections. Creating a better understanding of the functional pathways within the BG will allow researchers to explore more fully the relationship between the BG and other areas of the brain. For example, one symptom of Parkinson's disease is difficulty self-initiating movements, but if the patient is provided with visual cues the same movement can be made with ease. Understanding the interaction between the BG and the cerebellum may help us to understand these paradoxical movements (Glickstein and Stein, 1991).

3. BG disease results in diverse symptoms

Several disease states are associated with BG dysfunction. Some BG disorders manifest almost exclusively as motor difficulties, whereas others manifest as motor and cognitive difficulties. Combining clinical abnormalities with the known distribution of cortical inputs and outputs of the BG, it is clear that the BG participate in motor, cognitive, motivational and emotional behavior and that different disorders affect different elements of BG function. Below, we review 5 of the more common disease states linked to the BG.

Parkinson's Disease (PD) is characterized by a number of motor symptoms including rigidity, tremor, akinesia (a lack of movement) or a slowing of movement known as bradykinesia. The cause of PD is unknown but the symptoms result from the degeneration of DA neurons in the SNc. L-Dopa, the precursor to DA is the mainstay of medical treatment for PD. Nevertheless, for most patients after extended L-Dopa treatment, "on–off" symptoms appear in which the efficacy of L-Dopa becomes inconsistent and unpredictable. Symptoms of "on–off" syndrome include early morning akinesia, freezing episodes, peak-dose dyskinesia/akinesia, and end-of-dose deterioration (Marsden and Parkes, 1976). The influence of DA on target striatal neurons is receptor mediated, so the loss of DA is thought to result in an imbalance in the activity of the direct and indirect pathways (DeLong, 1990), but how the on-off syndrome develops is unknown. Because of the inconsistencies associated with drug therapy, the advent of DBS brought about a breakthrough in the treatment of PD. DBS was performed successfully in PD patients as early as 1987 (Benabid, 2003). Because one of DBS's major effects is minimizing the time spent in the 'off' state, when L-Dopa is not effective, DBS appears to play an important role in normalizing the activity of the BG. The mechanisms by which DBS acts as an effective treatment for PD remain largely unknown. Some research supports the idea that DBS is acting like a temporary lesion. Other results suggest that DBS acts by activating various pathways in the BG. In this issue, the article by Liu et al., titled "*High frequency deep brain stimulation: What are the therapeutic mechanisms?*" reviews the work in vitro and in vivo exploring the mechanisms of action of DBS. This review discusses evidence showing that DBS acts locally by inhibiting neuronal cell bodies and also acts long-distance by exciting output axonal fibers. In light of the results reviewed by Liu and colleagues, the answer to the controversial question "does DBS activate or does DBS inactivate" is yes. Translating modelling studies exploring how different patterns of stimulation can preferentially activate axons and cell bodies (Grill and McIntyre, 2001; McIntyre and Grill, 2002; McIntyre et al., 2004) into in vivo systems will go a long way to help us fine tune electrical stimulation for clinical as well as experimental purposes.

Huntington's Disease (HD) is known to result from a genetic mutation (Gusella et al., 1983). Onset usually occurs in mid-adulthood, and death generally follows about 10–15 years later. Characteristic symptoms of HD include choreiform movements (chorea means *dance* in Latin), which are involuntary spastic movements of the extremities. Subtle changes in mood and emotional state are often the initial signs of HD and as the disease progresses, severe dementia develops. Through some unknown mechanism, a mutation in the gene encoding the *Huntington* protein produces a degeneration of primarily the GABAergic medium spiny projection neurons in the striatum. Alterations of striatal output in turn disrupt proper functioning of the entire BG circuit. There is neither cure nor treatment for HD and the only intervention is symptomatic, using DA antagonists. The successful use of DBS for PD has prompted the exploration of DBS treatment for HD. Indeed, bilateral stimulation of GPi has been shown to improve motor symptoms in a patient with advanced HD (Moro et al., 2004). Whether or not the stimulation regime can slow the progression of HD is an exciting possibility that awaits future investigation.

Dystonia is characterized by extreme and contorted postures resulting from sustained co-contraction of skeletal muscle (Fahn et al., 1998). Some forms of dystonia are caused by a genetic mutation of the DYT1 gene that codes for torsinA, a chaperone protein, but how this mutation results in dystonia is unclear (Breakefield et al., 2001).

Dystonias can be generalized involving a significant portion of the musculature or focal involving a restricted group of muscles. One of the more commonly known focal dystonias occurs in the hands of highly skilled musicians or writers. Repetitive somatosensory stimulation of the fingers of monkeys (Wang et al., 1995) produces abnormal hand postures similar to those seen in humans with *writer's cramp*. The dystonia in monkeys was associated with an expansion of the representation of the fingers within the somatosensory cortex. This is found in humans with dystonia as well (Garraux et al., 2004). Indeed, in humans with dystonia, the receptive fields of neurons in GPi and thalamus are less selective than those seen in healthy monkeys (Lenz et al., 1999; Vitek et al., 1999). A recent post-mortem study suggests that the lesser understood pathway from the striatum back to the SNc (Graybiel et al., 2000) is damaged in the brains of dystonic patients (Goto et al., 2005). This observation is a clear demonstration that our conceptual models of BG need to incorporate the known anatomical pathways more fully. Clearly, a direction for future experiments will be to sort out the contribution of these lesser emphasized pathways to BG function in health and disease. In the paper contributed by Montgomery and Gale titled: "*Mechanisms of action of DBS*" the authors explore a radically new way of thinking about the BG. Rather than focusing on the anatomical conceptualizations, the authors suggest that the BG be viewed as a set of re-entrant loops with optimal oscillation frequencies for healthy movement. Further they propose that DBS may act by resonance effects through these loops.

Tourette Syndrome (TS) is often portrayed by the extreme cases in which people shout obscenities uncontrollably. The more common features of TS are uncontrollable blinking and facial grimacing. These repetitive movements that sometimes include vocalizations are called tics. They are often evoked by sensory stimuli and in some cases, by observing tics in other TS sufferers (Kushner, 1999). Imaging studies implicate several BG nuclei in TS, including the ventromedial caudate, putamen, and GP (Jeffries et al., 2002). Patients with chronic TS into adulthood may be treated with DA antagonists, but these are not always effective and often have undesirable side effects. DBS of specific thalamic nuclei is used to treat patients with chronic, treatment-resistant TS and is being met with very favorable results (Houeto et al., 2005; Temel and Visser-Vandewalle, 2004). While promising as a possible treatment option for TS, caution is advised since there are not long-term studies of the efficacy of this treatment for TS (Mink, 2004). Another challenge investigators of the BG face in the future is a thorough and mechanistic explanation of how cortico-striatal processing can produce symptomatology like that observed in TS (Mink, 2006). Despite the incredible advances that have been made in our understanding of BG function, many of which are described in this issue, TS reminds us that we still have much more to learn.

Obsessive-Compulsive Disorder (OCD) is diagnosed when a person engages in "recurrent obsessions or compulsions that are severe enough to be time consuming or cause marked distress or significant impairment". The symptoms cannot be explained by exposure to any substances or physical trauma (American Psychiatric Association, 2000). Anyone familiar with the life of aviator and billionaire, Howard Hughes, knows how incapacitating this disease can be. Imaging studies implicate the prefrontal-striatal loops in OCD (LaPlane et al., 1989). OCD like TS, points out that the BG influence neural systems extending well beyond motor control systems. For people with treatment-resistant OCD, neurosurgery is explored as a last resort (Greenberg et al., 2003; Jenike, 1998). With the introduction of DBS, electrical stimulation is providing a realistic treatment option for intractable OCD (Abelson et al., 2005). Drs. Kopell, and Greenberg, in their article "*Anatomy and physiology of the basal ganglia: Implications for DBS in psychiatry*," provide an in depth review of how DBS is used to treat OCD and other psychiatric disorders. They describe abnormalities in the BG-frontal cortex circuits, their correlation with clinical symptoms of OCD and how DBS is used to target these abnormalities. Also, in the article contributed by Chang and colleagues titled "*Studies of the neural mechanisms of deep brain stimulation in rodent models of Parkinson's Disease*" the authors show that electrical stimulation like that used for DBS can be interpreted by downstream structures differently depending upon behavioral context. For example, the pattern of activity in the SNr in response to high frequency stimulation of STN is different depending on whether an animal is engaged in an externally triggered or a self-initiated task. These two articles combined highlight that that BG is not just concerned with movement control and DBS may have implications extending far beyond just movement.

4. Hypotheses of BG function in health and disease

At least three hypotheses have dominanted our thinking about how BG function. Below, we introduce these three hypotheses briefly. The first we refer to as the parallel-pathway hypothesis, the second we refer to as the center-surround hypothesis, and the third is the temporal information processing hypothesis. None of these three hypotheses perfectly explains BG function in all normal and pathophysiological states, and none of the hypotheses is exclusive of the other two. The true function of the BG is likely to encompass aspects of all hypotheses.

A revolution in BG history came in 1989 and 1990 when Albin et al. (1989) and DeLong (1990) proposed a simple and elegant hypothesis, which we will refer to as the *parallel pathways hypothesis*, to understand how hypokinetic movement disorders such as PD, and hyperkinetic movement disorders such as HD, could result from BG pathology. The basic premise is that hypokinetic disorders result from overactivity of the GPi whereas hyperkinetic

disorders result from reduced activity of the GPi. In the healthy state, BG output is kept normal by balanced activity in the direct and indirect pathways. The parallel *pathways hypothesis* has fueled the successful treatment of PD in humans and of MPTP monkeys by pallidotomy and more recently, DBS of the STN. The shortcomings of the *parallel pathways hypothesis* are discussed in detail elsewhere (Obeso et al., 2000; Parent et al., 2000); however, one shortcoming is worth noting here because it played prominently in the development of a second hypothesis of BG function.

The *center-surround hypothesis* (Mink, 1996), incorporates neuroanatomical and physiological findings in monkeys and rodents, not addressed in the *parallel pathways hypothesis,* that demonstrate a fast, monosynaptic projection from the cerebral cortex to the STN, termed the hyperdirect pathway (Hartmann-von Monakow et al., 1978; Kitai and Deniau, 1981; Nambu et al., 2002). The inputs to the GPi arising from the STN form a dense plexus of terminals around the soma of GPi neurons whereas striatal inputs innervate proximal dendrites less densely (Parent and Hazrati, 1995b). In the *center-surround hypothesis*, the role of the striatal input is to provide a very focused inhibition of BG output nuclei (center) and the role of the STN input is to provide a widespread facilitation (surround). The result of this pattern of activity within the output nuclei on the target structures is to *disinhibit wanted movements* and *inhibit undesirable movements*. This model is attractive in part, because it accounts for dystonia and tics, two hyperkinetic disorders that are difficult to explain with the *parallel pathways hypothesis* (Albin et al., 1995). For dystonia, loss of D2 containing striatal neurons (Perlmutter et al., 1997) results in an insufficient surround inhibition at the level of the GPi (Mink, 2003). To explain TS, the *center-surround hypothesis* posits that there is abnormal activity in striatal neurons that leads to random patterns of disinhibition within the GPi (Mink, 2003). The predictions from this hypothesis remain to be tested in animal models. An important contribution of this hypothesis has been to emphasize the role of the BG in the healthy state, something that is difficult to understand from the *parallel pathways hypothesis* (Albin et al., 1995; Marsden and Obeso, 1994).

Both the *parallel pathways hypothesis* and the *center-surround hypothesis* share the assumption that the BG code information by the *rate* of neuronal discharge. This is reasonable since 30 years of work on motor systems shows that the average level of activity across an epoch of time often correlates well with movement parameters such as onset or velocity (for example, Fromm and Evarts, 1981). With the advent of multiple neuron recording techniques in behaving animals, however, it is becoming clear that information may also be coded by the relative timing of action potential occurrence among neurons and across brain areas. The *temporal information processing hypothesis* emphasizes the importance of temporal coding as a way to transmit information. For example, small groups of motor cortex neurons discharge action potentials closely in time (within 5 ms) and this spike synchronization correlates with sensory stimuli that evoke movements or even with cognitive events that predict movements. (Riehle et al., 1997, 2000). In healthy African green monkeys, GPi and GPe neurons discharge action potentials independently. After MPTP exposure, resulting in a loss of DA, GPi neurons discharge action potentials more closely in time and develop an oscillatory discharge pattern that correlates with tremor frequency (Raz et al., 2000). Indeed, GPi and STN neurons of PD patients exhibit oscillations that are modulated by L-Dopa treatment (Brown et al., 2001). Thus, it appears that information encoded by the relative timing of action potentials between neurons in the BG is an important factor that will need to be included in future models of BG function. In the article entitled "*Pathophysiology of the basal ganglia and movement disorders: From animal models to human clinical applications*," Israel and Bergman review the MPTP model of PD and in vivo electrophysiological experiments showing how this model has been indispensible for our understanding of the BG control of behavior. Further they emphasize and provide data to support the hypothesis that our focus on static models of BG function is inadequate to understand the myriad symptoms associated with BG disease. Rather, they emphasize that we should be more focused on dynamic models of BG function.

Following along the dynamic theme, the article contributed by Gale and colleagues titled: "*From symphony to cacophony: Pathophysiology of the human basal ganglia in Parkinson's Disease.*" provides an in depth review of all the current hypotheses of BG function and presents data suggesting that elements of each hypothesis can be found in some aspect of BG health and disease. The also provide yet a fourth hypothesis in which the BG and in particular DA, play a role in learning that is critical for normal BG function. In their article, the authors raise the interesting idea that different variations in symptoms may result from varying contributions of each of these hypothesized pathophysiologies.

5. Conclusions

The exact role played by the BG in behavior is still largely elusive. In this brief overview, we highlighted the anatomy and circuitry of the BG, reviewed common diseases associated with BG dysfunction and introduced the current state of conceptual models of BG function. We would be remiss if we failed to point out the tremendous progress that has been made in the field, in large part as a result of the initial *parallel pathways hypothesis*. The sheer volume of work generated from that conceptual model is singular. As we highlighted and shall see in the rest of this issue, it is not a complete model, but with new techniques and the continued interaction between basic science and clinical investigation, we are well-poised to develop more complete models in the near future.

The development of a complete model of BG function is not without challenges. Incorporating the temporal information processing hypothesis in a model of BG function will require researchers to determine how differences in temporal patterns correlate with the different aspects of BG dysfunction. Perhaps more far reaching is the need to determine how a temporal code translates into a rate code, since it is ultimately rate-coded motoneurons that are influenced by the BG. Indeed, this latter aspect applies to issues in Neuroscience more broadly as well. Perhaps in no other area of Neuroscience than the study of the BG has the confluence of basic science and clinical investigation been so fruitful. We hope that this issue continues that tradition.

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