# BASAL GANGLIA PATHWAYS:
# BEYOND THE CLOSED-LOOP CIRCUITS WITH THE CEREBRAL CORTEX

by

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Concepts of basal ganglia (BG) functions have been strongly influenced by their anatomical interconnections with the cerebral cortex. Views regarding these interconnections have changed dramatically over the past century. Specifically, advances in transneuronal tracing with neurotropic viruses have demonstrated that the BG participate in parallel closed-loop circuits with cerebral cortical areas that underlie motor and cognitive functions (Middleton and Strick, 2000b). Using transneuronal tracing techniques, we have identified two new pathways that allow the BG to influence motor and cognitive processes.

First, we used the retrograde transneuronal transport of rabies virus (RV) to show that the BG participates in open-loop circuits with the dorsal prefrontal cortex (PFC). Specifically, the ventral striatum (VStr) projects to the dorsal PFC, but does not receive input back from the dorsal PFC. Our results expand on the finding that there exist open-loop circuits between the BG and motor cortical areas (Kelly and Strick, 2004; Miyachi et al., 2006; Saga et al., 2011). These open-loop circuits provide a pathway for BG limbic processing to influence both motor and cognitive functions.

Second, we used retrograde transneuronal transport of RV to reveal a pathway that enables BG output to influence cerebellar (CB) function. Specifically, the subthalamic nucleus (STN) sends a disynaptic projection to the CB cortex. These results

are important because until recently, it was generally accepted that the BG and the CB were not directly connected. The pathway from the BG to the CB complements the recent discovery that the CB sends a disynaptic projection to the striatum (Hoshi et al., 2005). Together, these pathways provide the anatomical substrate for substantial interactions between the BG and the CB, in both the motor and nonmotor domains.

Overall, we identified two novel output pathways from the BG: from the VStr to the dorsal PFC and from the STN to the CB cortex. These pathways provide the BG with the potential to influence motor and nonmotor processes, outside of the traditional closed-loop circuits with the cerebral cortex. Considerable evidence suggests that these pathways are likely to have important effects on both normal and abnormal aspects of behavior.

**TABLE OF CONTENTS**

## LIST OF TABLES

## LIST OF FIGURES

## PREFACE

I would like to begin by thanking Peter Strick for being an amazing advisor. I have learned a great deal under his guidance and he has helped me grow both as a scientist and as a person. I would also like to thank the members of my dissertation committee: Rob Turner, Julie Fiez, Linda Rinaman and David Lewis for their time, interest, and feedback, and Okihide Hikosaka for accepting the role of external examiner.

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*"The basal "ganglia situated in the base of the brain still, to a large extent, retain the characteristics of basements – viz. darkness."*
- S. A. K. Wilson, 1925

*"In biology, if seeking to understand function, it is usually a good idea to study structure."*
– F. Crick & C. Koch, 2005

# 1.0 INTRODUCTION

Almost 350 years have passed since Thomas Willis first identified the basal ganglia (BG) and linked their function to the control of movement (Willis, 1664). Willis believed that the BG (termed the corpus striatum) received all sensory modalities and initiated all motor acts (Parent, 1986). Definite evidence for an association between the BG and movement has been available since 1912, when Kinnier Wilson discovered that lesions of the BG, in patients with hepatolenticular degeneration (Wilson's disease), caused abnormal involuntary movements (i.e., dyskinesias). Evidence for BG contributions to motor control has been accumulating ever since, but the nature of their contributions is still being debated (Aldridge et al., 2004; Desmurget et al., 2004; Doyon et al., 2009; Graybiel, 2008; Hikosaka et al., 2006; Houk et al., 2007; Lehéricy et al., 2005; Schmidt et al., 2008; Shadmehr and Krakauer, 2008; Tunik et al., 2009; Turner and Desmurget, 2010). There is a similarly long history of BG involvement in nonmotor processes. In his analysis of hepatolenticular degeneration, Wilson reported not only disturbances in motor function, but also "mental change or impairment" that "must not be underestimated" (Wilson, 1912). Notwithstanding these observations, the role of the BG in nonmotor function has been less easily accepted and the subject of considerable debate (Battig et al., 1960; 1962; Bhatia and Marsden, 1994; Brown et al., 1997; Cools et al., 1981; Hazy et al., 2007; Kawagoe et al., 1998; Marsden, 1980; 1981; Middleton and Strick, 2000b; Oberg and Divac, 1981). Advances in the knowledge of how the BG are interconnected with the rest of the brain, particularly with the

cerebral cortex, have both clarified the routes for BG involvement in motor control and solidified a role for these structures in nonmotor function.

The aim of this introductory chapter is twofold. First, it illustrates BG connections, primarily those with the cerebral cortex, in relation to their function. Second, it highlights important contribution of transneuronal tracing techniques to the current understanding of BG connections and functions. Towards these aims, the introduction will begin with an overview of the cortico-BG projection system in the primate and how it has been used to establish that segregated BG circuits process motor, associative, and limbic information (Parent and Hazrati, 1995a). This will be followed by a review of transneuronal tracing studies in primates and their contributions to the current conceptualization of BG connections and functions. Findings from these studies provide the impetus for the experiments that have been undertaken as part of this dissertation and are detailed in Chapters 2 and 3.

## 1.1 FUNCTIONAL ANATOMY OF THE BASAL GANGLIA

### 1.1.1 The basal ganglia

The term BG refers to a group of anatomically and functionally related subcortical nuclei. This group includes the striatum, the globus pallidus (GP), the substantia nigra (SN), and the subthalamic nucleus (STN). The striatum is formed by the caudate nucleus and the putamen. Unique connectivity patterns between ventral regions of the striatum and the limbic system mark the ventral striatum (VStr) as another distinct component of the striatum. The VStr includes the nucleus accumbens (NAcc) core and shell, the medial and ventral portions of the caudate nucleus

and the putamen, and the striatal cells of the olfactory tubercule (de Olmos and Heimer, 1999; Fudge et al., 2004). In the primate, the GP is formed by an external segment (GPe) and an internal segment (GPi). The GPe and GPi are homologues of the pallidum and entopeduncular nucleus in lower mammals. Additionally, the pallidal component that is closely linked with the VStr has been termed the ventral pallidum (VP). The SN is also a composite structure, formed by a dopaminergic dorsomedial portion (the pars compacta, SNpc) and a ventrolateral portion (the pars reticulata, SNpr) that histologically resembles the pallidum.

The BG can be construed as a hierarchical structure, consisting of input (striatum and STN) and output (GPi, VP, and SNpr) structures. The major source of afferents to the BG input layer is the cerebral cortex. The output structures of the BG send projections back to the cerebral cortex, via the thalamus. The emerging cortico-BG-thalamo-cortical loop is considered the main route by which the BG exercise their function and has been the focus of much scientific exploration (Parent and Hazrati, 1995a).

### 1.1.2 The cortico-striatal projection

The striatum is the main input structure of the BG and receives projections from the cerebral cortex, the thalamus, and brainstem regions. The massive projection from the cerebral cortex imposes a functional organization upon the striatum and subsequently, upon other BG structures. Therefore, knowledge of the detailed organization of the cortico-striatal projection is essential to determine the nature of information that is processed through BG circuits.

Most cerebral cortical areas have been shown to send projections to the striatum (Calzavara et al., 2007; Chikama et al., 1997; Flaherty and Graybiel, 1993; Haber et al., 1995; Kunishio and Haber, 1994; Künzle, 1975; 1977; Künzle and Akert, 1977; Parthasarathy et al.,

1992; Ragsdale and Graybiel, 1990; Saint-Cyr et al., 1990; Selemon and Goldman-Rakic, 1985; Stanton et al., 1988; Takada et al., 2001; Takada et al., 1998; Van Hoesen et al., 1981; Yeterian and Pandya, 1991; 1993; 1998; Yeterian and Van Hoesen, 1978). Kemp and Powell (1970) first proposed that cerebral cortical areas send topographically organized inputs to underlying striatal regions (i.e., anterior cortex to anterior striatum and posterior cortex to posterior striatum). Additional studies, however, have established that areas of the cerebral cortex project to parasagitally extended regions of the striatum (Goldman and Nauta, 1977; Selemon and Goldman-Rakic, 1985; Yeterian and Van Hoesen, 1978). Furthermore the topography of cortico-striatal projections appears to be driven by the functions of the cerebral cortical areas, rather than their geographical location. Specifically, projections from functionally related (adjacent or non-adjacent) cerebral cortical areas have terminal fields in nearby striatal regions (Selemon and Goldman-Rakic, 1985). Below, we will describe the main findings pertaining to the organization of projections to the striatum from functionally related regions in the sensorimotor, oculomotor, cognitive, and limbic domains.

Several areas in the cerebral cortex are considered to be motor areas, based on their physiological activity, their interconnections with each other, and their projections to the spinal cord (Dum et al., 2002; Dum and Strick, 1996; Picard and Strick, 1996; 2001). They include the primary motor cortex (M1), the supplementary motor area (SMA), the dorsal and ventral regions of the premotor cortex (PMd and PMv), and the cingulate motor areas. These motor areas project topographically to the striatum, mainly to regions of the putamen (Flaherty and Graybiel, 1994; Inase et al., 1999; Kemp and Powell, 1970; Künzle, 1975; Takada et al., 2001; Takada et al., 1998). M1 projects primarily to the dorsolateral putamen, caudal to the anterior commissure (Figure 1-1). Projections from the hindlimb, forelimb, and orofacial regions in M1 terminate in

dorsal, intermediate and ventral sections of the M1 receiving striatum. Projections from premotor cortical areas are adjacent to those from M1, and topographically organized in a similar fashion (Takada et al., 1998). Projections from the SMA target regions in the putamen that are partially overlapping with and medial to regions that receive M1 input. Projections from the PMd target more medial regions in the putamen that are partially overlapping with regions that receive SMA inputs, but not with regions that receive M1 inputs. The PMd projection extends more rostrally than that from M1 and slightly into the caudate nucleus. More rostral regions of the putamen have been shown to receive inputs from the cingulate motor areas (Takada et al., 2001). The same areas of the putamen receive projections from parietal areas associated with somatosensory function (Selemon and Goldman-Rakic, 1985). This array of inputs from the sensorimotor areas of the cerebral cortex, indicate that this region of the striatum has a role in motor function. Indeed, physiological and imaging studies support its involvement in sensorimotor control (Aldridge et al., 1980; Alexander et al., 1986; Lehéricy et al., 2006; Nambu et al., 2002; Worbe et al., 2009).

The frontal and supplementary eye fields (FEF and SEF) have been shown to project to a more central portion of the body of the caudate nucleus (Künzle and Akert, 1977). This region also receives projections from regions of the dorsolateral prefrontal cortex (PFC) and parietal cortex (Calzavara et al., 2007; Selemon and Goldman-Rakic, 1985; Stanton et al., 1988; Yeterian and Van Hoesen, 1978) that have been implicated in oculomotor mechanisms (Bizzi and Schiller, 1970; Goldberg and Bruce, 1986) and send projections to the superior colliculus (Fries, 1984; Leichnetz, 1981). Correspondingly, neurons in the caudate have complex visuomotor activities (Hikosaka et al., 1989a; Hikosaka et al., 2000). This area marks a transition in striatal

territory from a motor to a higher-order cognitive domain, as it also receives inputs from areas of the dorsolateral PFC that are closely associated with higher-order cognitive processing.

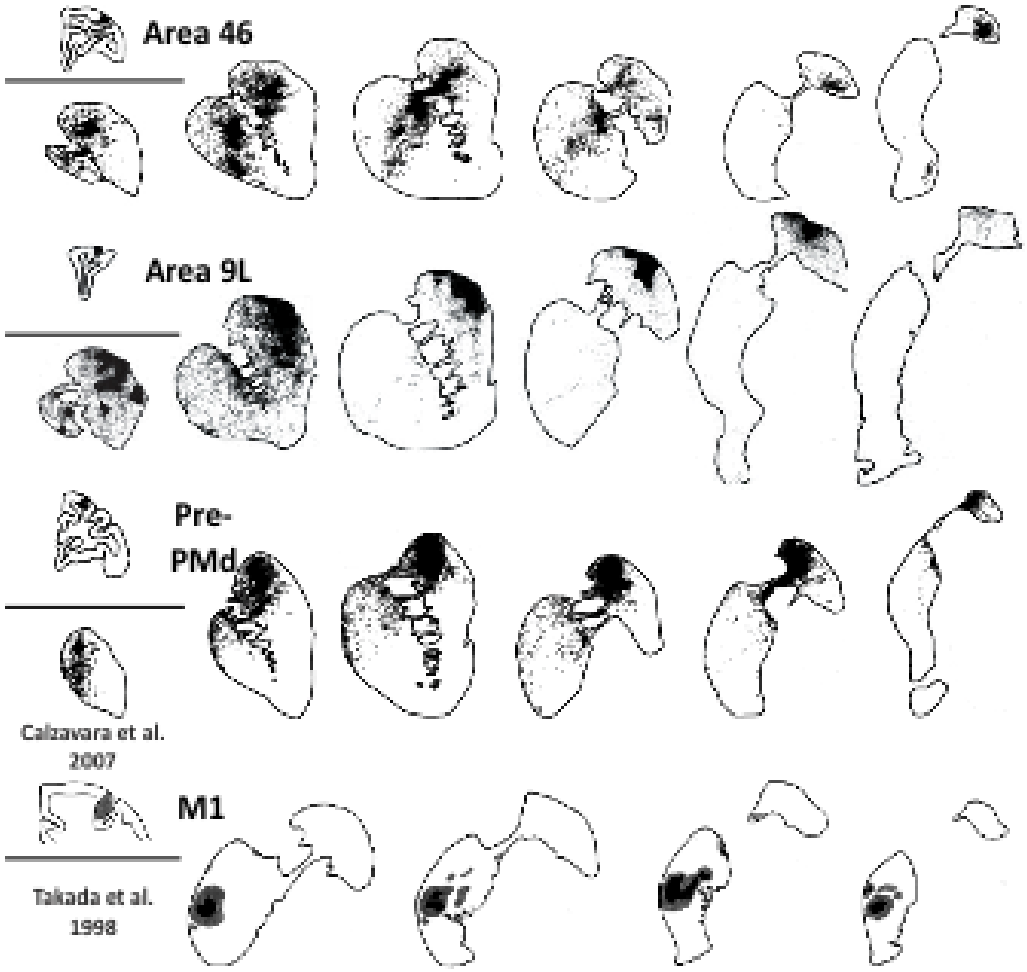


**Figure 1-1: Cortical projections to the striatum.**
Coronal sections through different rostro-caudal levels of the striatum display the distribution of terminals labeled after injections of anterograde tracers into dorsal prefrontal areas 46, 9L or PrePMd and into M1, from previously published data. Projections from these cortical area target distinct regions of the dorsal striatum. Each row depicts results from one cortical injection site. Injection sites are outlined on coronal sections of the cerebral cortex and shown at the top of each row. Pre-dorsal premotor cortex, PrePMd; M1, primary motor cortex. The top three rows have been adapted from Calzavara et al., 2007, with permission. The bottom row has been adapted from Takada et al., 1998, with permission.

Areas 9, 46, and Pre-dorsal premotor cortex (PrePMd) reach rostral regions of the dorsal striatum (including the caudate nucleus and the putamen) and target the entire rostrocaudal

extent of the caudate nucleus in a topographically organized fashion (Figure 1-1) (Calzavara et al., 2007; Yeterian and Pandya, 1991). Areas of the dorsal PFC have been involved in working memory, set shifting, and executive function (Goldman-Rakic, 1996; Smith and Jonides, 1997; 1999). Correspondingly, regions of the striatum that receive inputs from the dorsal PFC, the head of the caudate in particular, have been shown to be involved in cognitive functions, such as working memory (Apicella et al., 1992; Battig et al., 1960; 1962; Butters and Rosvold, 1968; Hikosaka et al., 1989b; Levy et al., 1997; Partiot et al., 1996; Scimeca and Badre, 2012).

Regions of the medial and orbital PFC send projections primarily to regions of the ventral striatum (VStr) in a topographically arranged fashion (Haber and McFarland, 1999). The lateral orbital regions, areas 13, 12, and the dysgranular insular cortex send projections to the central and lateral parts of the VStr (Chikama et al., 1997; Ferry et al., 2000; Haber et al., 1995; Kunishio and Haber, 1994). Medial orbital areas 13 and 14 project to the medial caudate and the NAcc, lateral to the shell region. The shell of the NAcc receives projections from medial areas 25, 32, and from the agranular insular cortex (Ferry et al., 2000; Freedman et al., 2000; Haber et al., 1995; Kunishio and Haber, 1994; Pandya et al., 1981). More posterior regions of the VStr, including medial aspects of the ventral putamen, medial regions and the tail of the caudate also receive inputs from association regions in the parietal and termporal cortical areas, especially regions in the anterior temporal cortex (Saint-Cyr et al., 1990; Van Hoesen et al., 1981; Yeterian and Pandya, 1993; 1998; Yeterian and Van Hoesen, 1978). As with the regions of the VStr considered previously, the inputs to the VStr provide useful guides to its function. Areas of the orbital PFC that project to the VStr have been involved in reward-based learning and goal directed behaviors (Butter and Snyder, 1972; Hikosaka and Watanabe, 2004; O'Doherty et al., 2001; Rolls, 2000; Schoenbaum and Roesch, 2005; Schoenbaum et al., 2006; Schoenbaum et al.,

2011; Tremblay and Schultz, 2000). Correspondingly, physiological and imaging studies demonstrate an important role for the VStr in the development of reward-based learning and in psychiatric disorders (Apicella et al., 1991; Bowman et al., 1996; Breier et al., 1992; Everitt et al., 1999; Hollerman et al., 2000; Koob and Volkow, 2010; Parkinson et al., 2000; Schultz et al., 1992; Schultz et al., 2000; Tremblay et al., 1998; Williams et al., 1993). Temporal cortical areas that send projections to the VStr, including the tail of the caudate have been involved in visual recognition and discrimination (Miyashita, 1993; Tanaka et al., 1991). Correspondingly, it has been shown that neurons in the tail of the caudate have visual responses (Brown et al., 1995; Caan et al., 1984; Yamamoto et al., 2012).

Importantly, unlike other regions of the striatum, the VStr receives projections from the amygdala and the hippocampus (Fudge et al., 2004; Fudge et al., 2002; Russchen et al., 1985). There is a topography of amygdaloid inputs to the VStr: the shell receives inputs from the central amygdaloid nucleus and the periamygdaloid nucleus, as well as the basal and accessory basal nuclei, while regions outside the shell are mainly influenced by the basal and accessory basal nuclei (Fudge et al., 2002). Overall, inputs from amygdaloid nuclei reach widespread ventral regions throughout the rostro-caudal extent of the striatum and have been useful in defining the extent of the VStr (Figure 1-2) (Fudge et al., 2004; Fudge et al., 2002).

To summarize, cortico-striatal projections impose a broad functional organization in the striatum. Based on its cortical inputs, the striatum has been divided into a sensorimotor territory that processes sensory and motor information, an associative territory that processes cognitive information, and a limbic territory that processes emotional and motivational information (Parent and Hazrati, 1995a). The exact borders between these territories are not perfectly clear, but it has become generally accepted that the sensorimotor territory comprises the dorsolateral portion

of the putamen, posterior to the anterior commissure, and the dorsolateral portion of the head of the caudate, which receive inputs from sensory and motor regions of the cerebral cortex (Inase et al., 1999; Kemp and Powell, 1970; Künzle, 1975; Takada et al., 1998; Tokuno et al., 1999). The associative territory comprises large parts of the putamen, rostral to the anterior commissure, and most of the caudate nucleus, which receive inputs from association regions of the frontal, temporal, and parietal lobes (Calzavara et al., 2007; Yeterian and Pandya, 1991; 1993; Yeterian and Van Hoesen, 1978). The limbic territory overlaps with the VStr, including the NAcc, portions of the olfactory tubercule, and ventral and medial parts of the caudate and the putamen, which receive inputs from limbic areas of the cerebral cortex (Chikama et al., 1997; Freedman et al., 2000; Haber et al., 1995; Kunishio and Haber, 1994; Pandya et al., 1981; Yeterian and Pandya, 1991), but also from higher order visual areas (Saint-Cyr et al., 1990; Webster et al., 1993; Yeterian and Pandya, 1998; Yeterian and Van Hoesen, 1978) and from the amygdala and hippocampus (Figure 1-2) (Fudge et al., 2004; Fudge et al., 2002; Russchen et al., 1985).

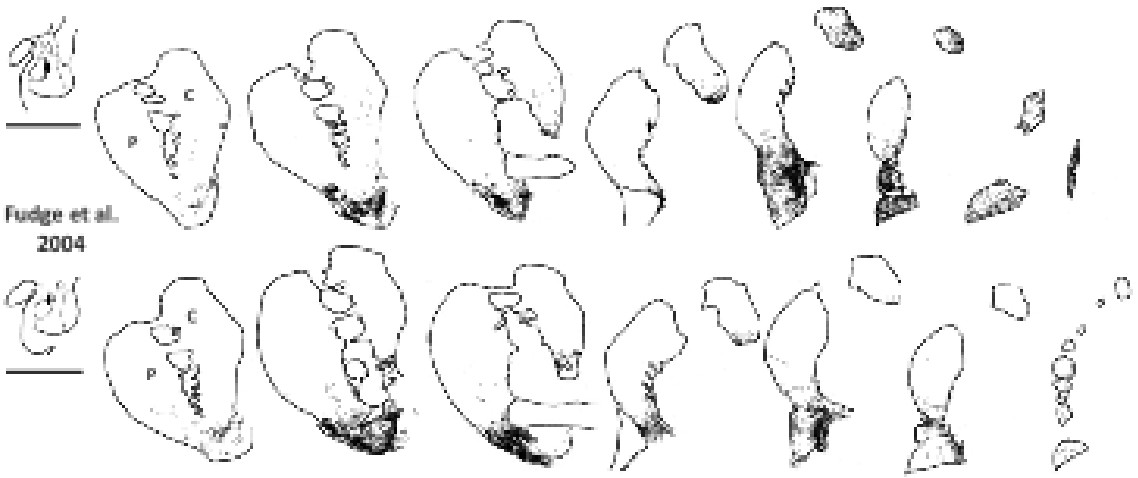


**Figure 1-2: Amygdala projections to the striatum.**

Coronal sections through different rostrocaudal levels of the striatum display the distribution of terminals labeled after injections of anterograde tracers into two amygdaloid nuclei: the basal nucleus, magnocellular subdivision (top), and the accessory basal nucleus, magnocellular subdivision (bottom), from previously published data. Injection sites are outlined on coronal sections of the amygdala and shown at the top right of each row. C, caudate; P, putamen. From Fudge et al., 2004, with permission.

As mentioned above, the striatum is also known to receive thalamic inputs. It receives considerable projections from midline and intralaminar nuclei (Fenelon et al., 1991; François et al., 1991; Jones and Leavitt, 1974; Nakano et al., 1990; Nakano et al., 1999; Sadikot et al., 1990; 1992) and from the mediodorsal (MD), ventral anterior (VA) and ventral lateral (VL) nuclei (Druga et al., 1991; Giménez-Amaya et al., 1995; McFarland and Haber, 2000; 2001). Thalamic nuclei that are interconnected with motor, association, and limbic regions in the cerebral cortex send projections to corresponding regions in the striatum (McFarland and Haber, 2000; 2001), preserving its functional topography. Similarly, the connections between the striatum and other BG structures perpetuate the segregation between the sensorimotor, associative, and limbic pathways (Parent and Hazrati, 1995a; b).

### 1.1.3 Intrinsic basal ganglia circuits

Projections to the striatum synapse predominantly on dendritic spines of medium spiny neurons (MSN) (Kemp and Powell, 1970). There are also important dopaminergic projections from the SNpc onto the necks of MSN dendritic spines, regulating the effects of cortical and thalamic inputs to the striatum (Smith and Bolam, 1990). Dopaminergic inputs are also critical in defining two main pathways of information processing through the striatum and subsequent BG circuits (Albin et al., 1989; DeLong and Wichmann, 2009; 2010; DeLong, 1990; DeLong and Wichmann, 2007; Penney and Young, 1986). The *direct* pathway is a monosynaptic inhibitory projection from MSNs that contain substance-P and dopamine D1 receptors to GPI/SNpr neurons. The *indirect* pathways is a multisynaptic projection that involves an initial inhibitory projection from MSNs that express enkephalin and dopamine D2 receptors to the GPe, and then direct inhibitory projections from the GPe to the GPi/SNpr, or indirect projections from the GPe

to the GPi/SNpr, through the glutamatergic STN. Although a complete dissociation between the direct and indirect pathways has been challenged by anatomical studies (Parent et al., 2001), they are still believed to play key roles in the normal function and pathophysiology of the BG (Wichmann et al., 2011).

It has been shown that striatal projections to the GPe, GPi, and SNpr maintain a clear topographical organization and interconnected sensorimotor, associative, and limbic regions can be identified in all of these BG structures (Alexander et al., 1986; Carpenter et al., 1981; Haber et al., 1990; Hedreen and DeLong, 1991; Lynd-Balta and Haber, 1994; Nauta and Mehler, 1966; Parent and Hazrati, 1995a; b; Selemon and Goldman-Rakic, 1990; Szabo, 1967; 1970). Briefly, projections from the sensorimotor areas of the striatum terminate in the ventrolateral part of GPe and GPi and in the ventrolateral SNpr. Projections from the central striatum terminate in more central regions of the GPe, GPi, and SNpr. Projections from the VStr terminate in the VP and dorsal SNpr.

Pallidal projections to the STN support a topographical organization within this structure as well, dividing the STN into a dorsolateral motor area, a central associative area, and a medial limbic component (Haber et al., 1993; Karachi et al., 2005; Parent and Hazrati, 1995b; Shink et al., 1996). Direct projections from the cerebral cortex to the STN are in rough correspondence with this arrangement: motor areas target dorsal regions of STN in a somatotopically organized manner, the FEF targets a lateral portion of the STN, regions of the dorsolateral PFC send projections to more ventral and central portions of the STN, while rostral and ventral regions of the PFC target medial regions of the STN, some of which extend outside traditional borders of the nucleus (Haynes and Haber, 2013; Inase et al., 1999; Monakow et al., 1978; Nambu et al., 1996; Nambu et al., 1997; Stanton et al., 1988). The direct projection from the cerebral cortex to

the STN is considered the source of another important pathway through the BG, the *hyperdirect* pathway, which is believed to convey powerful excitatory effects from the cerebral cortex to the GPi, with shorter conduction times than the direct or indirect pathways through the striatum (Nambu et al., 2000).

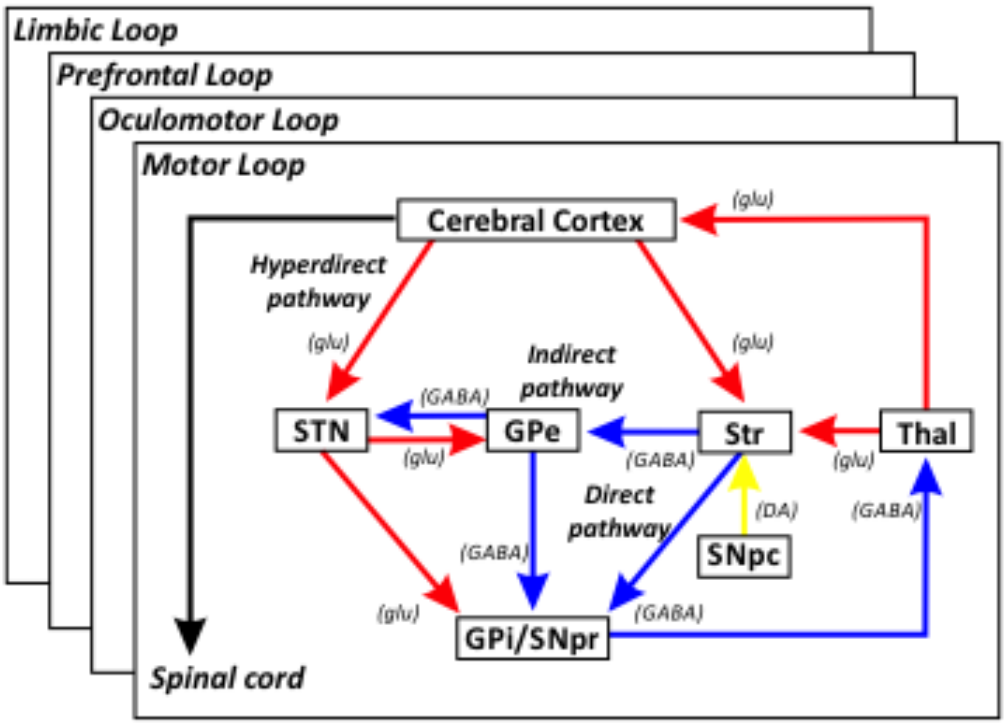


**Figure 1-3: Basic circuitry of the basal ganglia.**
Red and blue arrows indicate excitatory and inhibitory projections, respectively. Yellow arrow indicates the dopaminergic projection. DA, dopamine; GABA, gamma-aminobutyric acid; glu, glutamate; GPe and GPi, external and internal segments of the globus pallidus; SNpc, substantia nigra pars compacta; SNpr, substantia nigra pars reticulata; STN, subthalamic nucleus; Str, striatum; Thal, thalamus. Based on Nambu 2011.

To summarize, three main pathways have been proposed that enable information transfer from the cerebral cortex through the BG: the direct, indirect, and hyperdirect pathways (Figure 1-3). The interconnections between BG structures may be more complex than this framework suggests, but they maintain a clear topographical organization that reflects that of the cerebral

cortex. This organization has been the basis for the parallel processing hypothesis (Alexander et al., 1986), which states that information from different cortical areas is processed independently through the BG. In the next section, we will discuss this hypothesis and the anatomical evidence that supports it.

## 1.2 BASAL GANGLIA LOOPS WITH THE CEREBRAL CORTEX

### 1.2.1 Transneuronal tracing with neurotropic viruses

Early accounts of BG connections with the cerebral cortex held that the BG serves to funnel all the information it receives from widespread areas of the cerebral cortex back, via the ventrolateral thalamus, to a single cortical area, M1 (Figure 1-4) (Kemp and Powell, 1971). As detailed in the previous section, subsequent studies of the BG do not support the notion that they are sites where inputs from functionally distinct areas of the cerebral cortex converge. Instead, circuits within the BG appear to process parallel streams of information. Furthermore, evidence indicates that BG output reaches several different subdivisions of the thalamus (Percheron et al., 1996), which in turn project to a wide variety of areas (not only to M1). Based on these results, Alexander, DeLong and Strick (1986) proposed that the BG process segregated streams of information and transmit each stream back to the area of the cerebral cortex that initiates it. These closed-loops form multiple parallel circuits between the BG and the cerebral cortex (Middleton and Strick, 2000a; b; Middleton and Strick, 2002). Therefore, the outputs from the BG could influence not only the control of movement, but also higher order cognitive and limbic functions.

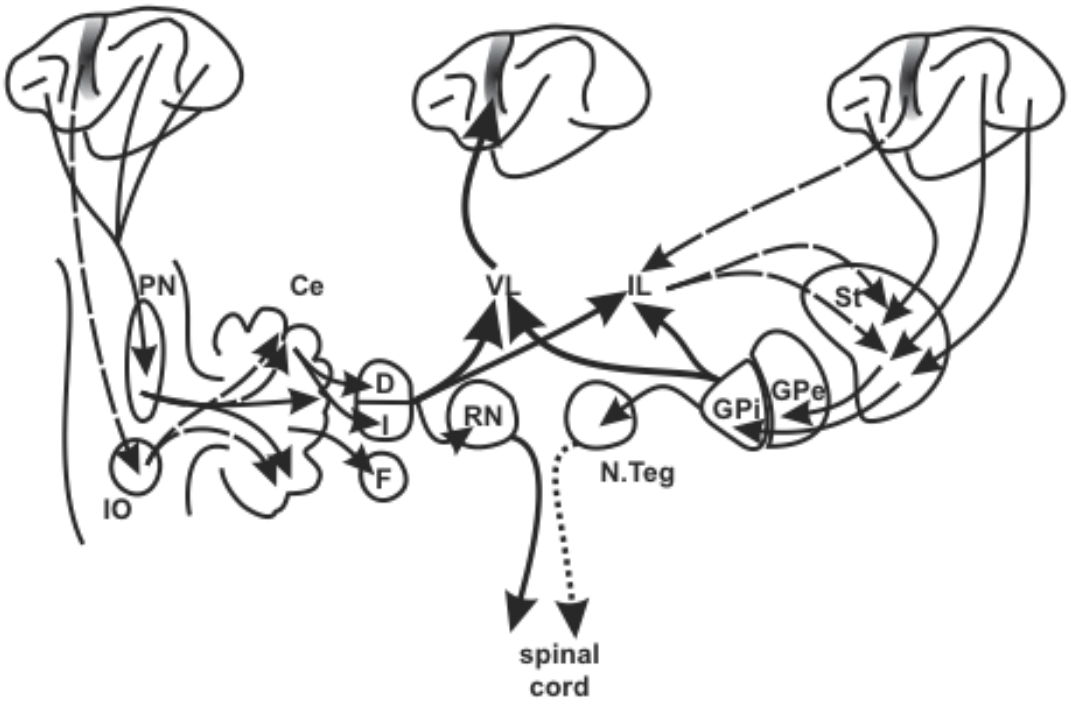


**Figure 1-4: Traditional view of basal ganglia and cerebellar connections with the cerebral cortex.**
Schematic figure summarizes the traditional view of basal ganglia and cerebellar connections with the cerebral cortex. Presumably equivalent pathways in the two systems are shown by the same kinds of symbols. Interrupted lines indicate possible connections. Ce, cerebellar cortex; D, dentate nucleus; F fastigial nucleus; GPe and GPi, external and internal segments of the globus pallidus; IO, inferior olive; N.Teg, tegmental nuclei; PN, pontine nuclei; RN, red nucleus; St, striatum; VL, ventrolateral nucleus of the thalamus. Based on Kemp and Powell, 1971, adapted from DeLong and Wichmann, 2010.

The use of neurotropic viruses as transneuronal tracers has been essential for solidifying this proposal, because of their ability to reveal multiple links in a chain of synaptically connected neurons (Dum and Strick, 2012). The findings detailed in the previous section used conventional anterograde and retrograde tracers to determine the organization of BG circuits. Conventional anterograde tracers indicate the site of termination of axons from an injection site, but do not identify the specific neurons that are the targets of these axons. Conventional retrograde tracers only identify the neurons that send direct projections to an injection site. The nature of these tracers limits the interpretations of the data from studies of complex circuits, such as those linking the BG with the cerebral cortex.

For example, based on conventional tracer studies we know that a region of the cerebral cortex sends projections to a specific region of the striatum, that the same region of the striatum sends projections to a specific region in the GPi and that output from the GPI reaches thalamic nuclei that send inputs to the cerebral cortex. Does this mean that individual striatal neurons project to neurons in the GPi that synapse onto thalamic neurons that send projections to the cerebral cortex? Based on the conventional tracer data, we can hypothesize that this is the case, but we cannot be certain. Additional dual-labeled conventional tracers experiments or neurophysiologic techniques are needed to provide proof of synaptic connections between chains of three interconnected neurons. Such experiments have been used to confirm the pathway from the GPi to M1, PMd and SMA via the thalamus (Inase and Tanji, 1994; Jinnai et al., 1993; Nambu et al., 1988; Sakai et al., 1999).

The use of neurotropic viruses has greatly facilitated the scientific efforts to establish the targets of BG outputs. Neurotropic viruses are exceptionally useful for tracing complex circuits because they move from neuron to neuron exclusively at synapses, in a time-dependent fashion (Dum and Strick, 2012; Kelly and Strick, 2000; Ugolini, 1995; Ugolini, 2010). Careful adjustment of the survival time after a virus injection allows for the study of neural circuits composed of two (second-order), three (third-order), four (fourth-order) or more synaptically connected neurons (Kelly and Strick, 2004). Selected strains of virus move transneuronally in either the retrograde or anterograde direction (Kelly and Strick, 2003). Thus, one can examine either the inputs to or the outputs from a site. The following sections will detail a series of studies using transneuronal tracers to identify first, the regions of the cerebral cortex that receive BG output and second, the macro-architecture of BG circuits with the cerebral cortex.

### 1.2.2 Basal ganglia outputs to motor and nonmotor regions of the cerebral cortex

Neurotropic viruses have been used to demonstrate that the BG sends outputs not only to motor regions of the cerebral cortex, but also to nonmotor areas of the frontal, parietal, and temporal lobes (Figures 1-5 and 1-6). Retrograde transneuronal transport of the herpes simplex virus type 1 (HSV1) was first used to examine the organization of BG outputs to M1 (Hoover and Strick, 1993; 1999). In separate animals, HSV1 was injected into either the arm, leg, or face regions of M1. The survival time was set to allow retrograde transport of the virus from the injection site to first-order neurons that project to the injection site (i.e. neurons in the thalamus), and then retrograde transneuronal transport from the first-order neurons to second-order neurons that are the origin of BG output to M1. These experiments provided evidence for disynaptic projections from the output nuclei of the BG to M1. The densest projections to M1 originate from GPi, but some projections from SNpr were also observed. Additionally, labeling in GPi was somatotopically organized, with separate regions of GPi labeled after injections to the arm, leg, or face (Figure 1-7). These data provided the first evidence for somatotopically organized, parallel BG output channels. Interestingly, GPi projections to M1 originated from a restricted portion within the GPi motor territory and comprised only 15% of the volume of GPi. This limited territory for one output channel suggests that the majority of output from BG is directed to other areas of the cerebral cortex, as predicted by the parallel processing hypothesis (Alexander et al., 1986).

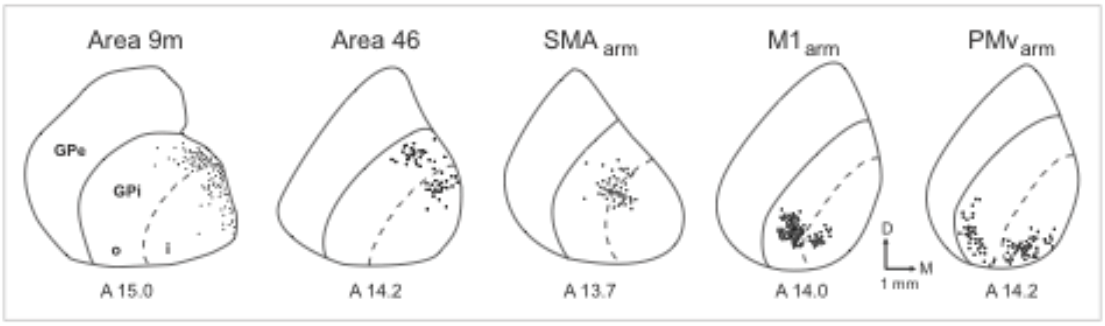


**Figure 1-5: Origin of pallidal projections to M1, PMv, SMA, area 46, and area 9.**
Labeled neurons (dots) from several adjacent sections are displayed on coronal sections through the GPi of animals that received virus injections into different cortical areas. The anterior-posterior location of each section is indicated. GPe and GPi, external and internal segments of the globus pallidus; o, outer portion of the internal segment of the globus pallidus; i, inner portion of the internal segment of the globus pallidus; M1 arm, arm area of the primary motor cortex; PMv arm, arm area of the ventral premotor area; SMA arm, arm area of the supplememntary motor area. From Middleton and Strick, 2000b, with permission.

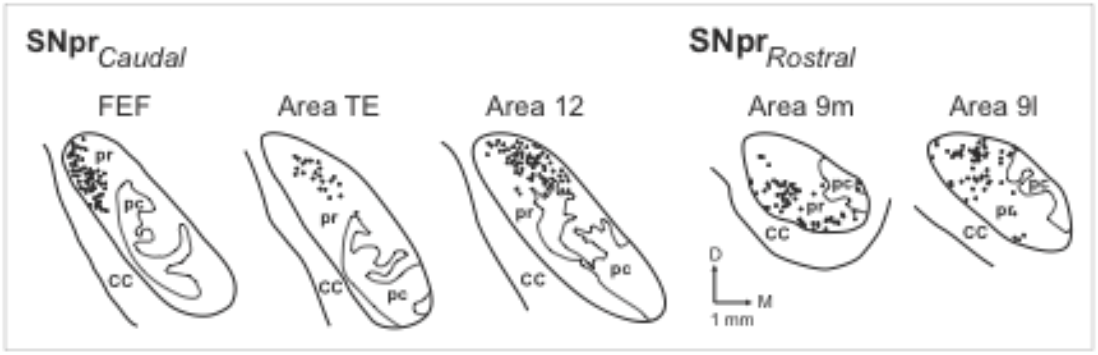


**Figure 1-6: Origin of nigral projections to the FEF, areas TE, 12, 9m, and 9l.**

Coronal sections indicating the location of labeled neurons in the caudal and rostral sections of the SNpr following injections into different cortical areas. D, dorsal; FEF, frontal eye fields; M, medial; pc, pars compacta; SNpr, substantia nigra pars reticulata. From Middleton and Strick, 2000b, with permission.

BG projections to the arm representations of premotor areas in the frontal lobe were examined following injection of HSV1 into PMv and SMA (Akkal et al., 2007; Hoover and Strick, 1993). These injections consistently labeled neurons in the middle of GPi rostrocaudally. Within this region, neurons labeled after injections into SMA, M1, or PMv, formed separate clusters in a dorsal to ventral arrangement (Figure 1-5). These observations confirm that GPi output targets not only M1, but also several other motor areas. Additionally, the arm representations of each of the investigated motor areas receive input from a restricted region in the GPi (Figure 1-7). This result suggests that GPi output to motor areas of the frontal lobe is somatotopically organized.

BG projections to the FEF were also investigated using the transneuronal transport of HSV1. Virus was injected into FEF regions where eye movements were evoked by intracortical stimulation (Lynch et al., 1994). Within the BG, these injections labeled neurons in the posterior and lateral portions of the SNpr (Figure 1-6). Neurons in these regions of SNpr display changes in activity related to saccadic eye movements (Hikosaka and Wurtz, 1983a; b). Importantly, this oculomotor output channel from the BG is anatomically distinct from those reaching the skeletomotor areas in the frontal lobe.

Similar findings have been demonstrated for regions of the PFC (Figure 1-5 and 1-6). Virus injections into areas 9, 12, and 46 labeled numerous neurons in the output nuclei of the BG (Middleton and Strick, 1994; Middleton and Strick, 2002). Injections into area 12 labeled neurons in a localized portion of the SNpr. In contrast, injections into area 46 labeled neurons largely in the associative territory of the GPi. Area 9 injections labeled neurons in both SNpr and GPi. The topographic nature of BG projections to PFC is further emphasized by the finding that different regions within the rostral SNpr project to medial and lateral portions of area 9.

Importantly, in all cases of PFC injections, the locations of neurons labeled in GPi and SNpr are different from those labeled after injections into motor areas of the cerebral cortex. These results support a division between motor and nonmotor (associative) domains within GPi (Figure 1-7).

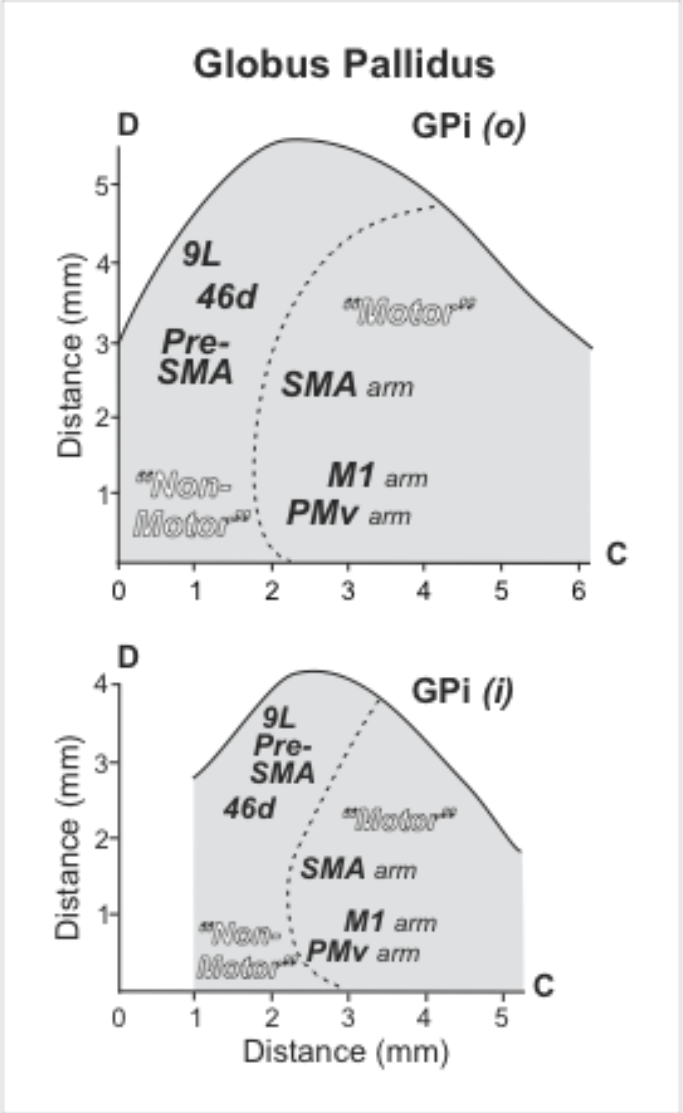


**Figure 1-7: Summary map of pallidal output channels.**

The outer and inner segments of the GPi are shown as separate unfolded maps. In this planar view, the cortical target of each output channel is placed at its densest labeling following retrograde transneuronal transport of virus from that cortical area. The GPi can be divided into motor and nonmotor domains based on the grouping of output channels that target functionally similar cortical areas. GPi, internal segment of the globus pallidus; PreSMA, pre-supplementary motor area; o, outer portion of the internal segment of the globus pallidus; i, inner portion of the internal segment of the globus pallidus; M1 arm, arm area of the primary motor cortex; PMv arm, arm area of the ventral premotor area; SMA arm, arm area of the supplememntary motor area. Adapted from Akkal et al., 2007, with permission.

The Pre-supplementary motor area (PreSMA) and PrePMd have traditionally been included with the motor areas of the frontal lobe. However, several observations emphasize the nonmotor contributions of these areas (Picard and Strick, 2001). For example, unlike the cortical motor areas, the PreSMA and PrePMd do not project to M1 or the spinal cord. Virus tracing was used to examine whether BG outputs to PreSMA originate from the motor or the nonmotor domains of the GPi (Akkal et al., 2007). Virus injected into PreSMA labeled neurons dorsally in the rostral GPi, adjacent to regions that project to PFC (Figure 1-7). These observations provide further support of the proposal that the PreSMA is more similar to regions of the PFC than to the premotor areas (Picard and Strick, 2001).

Virus tracing further demonstrated that the sphere of influence of BG output extends to include portions of the posterior parietal and inferotemporal cortex. Specifically, a portion of area 7b in the intraparietal sulcus and area TE in the inferotemporal cortex have been shown to be targets of output from SNpr (Clower et al., 2005; Middleton and Strick, 1996). Regions of the SNpr that project to area TE appear to be separate from regions that influence the FEF or subdivisions of the PFC (Figure 1-6). TE is known to play a critical role in the visual recognition and discrimination of objects (Miyashita, 1993; Tanaka et al., 1991). Physiological studies have shown that regions of SNpr that send outputs to TE contain neurons that respond to visual stimulation (Hikosaka and Wurtz, 1983a). Projections from BG to TE and the parietal cortex provide evidence that BG output is involved in higher order aspects of visual processing, as well as in motor and cognitive functions.

To summarize, experiments using transneuronal transport of neurotropic viruses have demonstrated that, as predicted by Alexander, DeLong and Strick (1986), the BG can access

more widespread and diverse areas of the cerebral cortex than previously imagined. To date, these studies have shown that BG output nuclei project, via the thalamus, to skeletomotor, oculomotor, prefrontal, posterior parietal, and inferotemporal cortical areas. These projections originate in segregated regions of the BG output nuclei, maintaining the topographical organization imposed onto the BG by projections from the cerebral cortex. Overall, these data demonstrate that the anatomical substrate exists for the BG to influence higher order aspects of cognition, such as sequencing, planning, working memory, visuospatial processing and attention as well as somatomotor and oculomotor functions.

### 1.2.3 Macroarchiatecture of basal ganglia loops with the cerebral cortex

Considerable evidence supports the concept that areas of the cerebral cortex that receive output from the BG also project to BG input nuclei. These observations are in agreement with the hypothesis that the parallel pathways linking the BG with the cerebral cortex are closed-loop circuits (Alexander et al., 1986). Studies using the transneuronal transport of neurotropic viruses have further reinforced this hypothesis by demonstrating that the sites within the input structures of the BG (the striatum and the STN) that receive direct inputs from an area of the cerebral cortex are in register with the (third-order) neurons that ultimately project back to the same area of the cerebral cortex.

Comparisons between the inputs to and outputs from the striatum and STN have been conducted for M1, PMd, and area 46 in the PFC (Kelly and Strick, 2004; Miyachi et al., 2006; Saga et al., 2011). These studies have used retrograde transneuronal transport of rabies virus (RV) into M1, PMd, and area 46 and allowed for third-order transport of the virus from the injection sites to neurons in the striatum and the STN. Within the striatum, regions that receive

the major projection from the sensorimotor cortex (Inase et al., 1996; Künzle, 1975; Takada et al., 1998) contain third-order neurons that project to M1 (Figure 1-8) (Kelly and Strick, 2004). Furthermore, this third-order labeling from M1 is somatotopically arranged in accordance with the cortico-striatal inputs: hindlimb, orofacial, and forelimb RV injections labeled neurons in dorsal, ventral, or intermediate zones of the putamen, respectively (Miyachi et al., 2006).

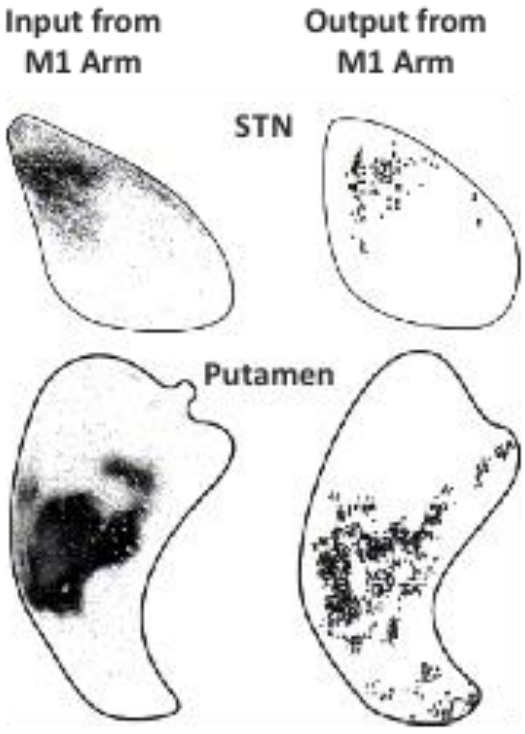


**Figure 1-8: Open- and closed-loops between the basal ganglia and M1 arm.**

Top row shows the closed-loop organization in the STN. On the left, efferents from M1 arm are shown on an STN section. On the right, third-order rabies virus (RV) neurons (dots) define the location of projections from the STN to M1 arm. Note that the region of STN that receives input from M1 overlaps with the region that projects to M1. Bottom row shows the closed- and open-loop organization in the putamen. On the left, efferents from M1 arm are shown on a section through the putamen. On the right, third-order RV neurons (dots) define the location of projections from the putamen to M1 arm. Note that there is extensive overlap between the region of the putamen that receives input form M1 and the region that projects to M1. However, there are neurons labeled in the ventral putamen in regions that do not receive input from M1. M1 arm, the arm area of the primary motor cortex; STN, subthalamic nucleus. From Kelly and Strick, 2004, with permission.

A similar input-output arrangement is apparent in the STN (Figure 1-8). The dorsolateral region of the nucleus where third-order neurons that project to M1 are labeled, receives input from M1 (Monakow et al., 1978; Nambu et al., 1996). Similarly, the regions of STN where third-order neurons that project to the PMd and area 46 are labeled have been shown to receive inputs from these areas of the cerebral cortex (Monakow et al., 1978; Nambu et al., 1997). Therefore, an important component of interconnections between motor and prefrontal regions of the cerebral cortex and the input nuclei of the BG are characterized by closed-loop macro-architectures.

In their analysis of the correspondence between M1 input and output in the striatum and STN, Kelly and Strick (2004) noted that the match is not always complete (Figure 1-8). They observed that along with labeling in the sensorimotor arm region of the striatum, virus injections into arm M1 labeled a dense group of third-order neurons in ventral regions of the putamen. The ventral putamen does not receive input from M1, indicating that an open-loop pathway from the striatum to M1 also exists. The existence of this open-loop has also been demonstrated for other M1 regions (hindlimb and orofacial) and for the PMd (Miyachi et al., 2006; Saga et al., 2011). The open-loop component of cortico-BG pathways with motor areas of the cerebral cortex provides a way for the limbic circuit in the BG to influence motor processing in the cerebral cortex. Several important questions about this open-loop component remain to be addressed.

First, the VStr does not project to regions of GPi/SNpr that reach M1 (i.e., portions of GPi/SNpr labeled in second-order virus tracing experiments). Consequently, the VStr projections to M1 are unlikely to be processed through the traditional BG-thalamo-cortical route. What alternative pathway is most likely utilized for this open-loop connection? Second, the closed-loop architecture has been demonstrated for BG connections with both motor and

nonmotor areas of the cerebral cortex. Is the open-loop architecture a unique feature of the BG connections with motor areas, or does it also apply to BG connections with nonmotor regions, such as areas of the PFC? Third, the closed-loop component of BG interactions with the cerebral cortex has a clear topographical organization. For example, the closed-loop connection between the sensorimotor striatum and M1 has been shown to be somatotopically organized (Miyachi et al., 2006). If the open-loop projection from the VStr includes nonmotor regions of the cerebral cortex, are VStr projections to motor and nonmotor regions segregated? Finally, the relative strength of the open-loop component is unknown. Is this projection prominent enough to have important functional consequences? In Chapter 2, we will describe results from a series of experiments aimed at addressing these questions. These results provide us with significant insights into the characteristics of the open-loop component of BG circuits with the cerebral cortex.

## 1.3 THE CEREBELLUM COMMUNICATES WITH THE BASAL GANGLIA

### 1.3.1 Cerebellar circuits with the cerebral cortex

Similar to the BG, the traditional view of the cerebellum (CB) was that it received information from widespread areas of the cerebral cortex, performed sensorimotor transformations on its inputs, and provided output exclusively to the primary motor cortex, via the ventrolateral thalamus (Figure 1-4) (Allen and Tsukahara, 1974). It is now clear that efferents from the deep cerebellar nuclei (CBN) project to multiple subdivisions of the thalamus (Percheron et al., 1996), which, in turn, project to a myriad of neocortical areas, including premotor, prefrontal, and

posterior parietal areas of the cerebral cortex (Strick et al., 2009). Moreover, recent findings have shown that the CB projects disynaptically to the BG (Hoshi et al., 2005). This section will briefly address the anatomical organization of the CB, based on its interconnections with the cerebral cortex, as background for discussing its connections to the BG.

The use of neurotropic viruses as transneuronal tracers has been essential for the identification of the areas of the cerebral cortex that are the targets of CB output (Akkal et al., 2007; Clower et al., 2005; Clower et al., 2001; Dum et al., 2002; Dum and Strick, 2003; Hoover and Strick, 1993; 1999; Kelly and Strick, 2003; Lynch et al., 1994; Middleton and Strick, 1994; Middleton and Strick, 2001; Prevosto et al., 2010; Schell and Strick, 1984; Strick et al., 2009). These studies have shown that CB projections to M1 originate largely from neurons in the dentate nucleus. Furthermore, there is a rostral to caudal sequence for dentate output to the leg, arm, and face representations in M1 that corresponds well with the somatotopic organization of the dentate previously proposed on the basis of physiological studies (Allen et al., 1978; Rispal-Padel et al., 1982; Stanton, 1980). Besides its outputs to M1, the dentate has been shown to send projections to other motor areas in the frontal lobe, as well as regions of the prefrontal and posterior parietal cortex (Clower et al., 2005; Kelly and Strick, 2003; Middleton and Strick, 1994; Prevosto et al., 2010). When the results of all these experiments are considered together, it is clear that the dentate contains distinct output channels that project to areas 9m, 9l, 46d, 7b, the anterior intraparietal area (AIP), medial intraparietal area (MIP), and the ventral lateral intraparietal area (LIPv), but not to areas 12, 46v, 7a, or TE. The output channels to PFC are clustered together in a ventral region of the nucleus that is entirely outside the more dorsally located motor domain. The division of the dentate into separate motor and nonmotor domains (Figure 1-9) is reinforced by underlying molecular gradients within the nucleus of monkeys

(Akkal et al., 2007; Dum et al., 2002; Fortin et al., 1998), different evolutionary trajectories in the development of the dorsal and ventral dentate (Matano, 2001), and imaging studies in humans (Allen et al., 2005; Habas, 2010; Habas et al., 2009).

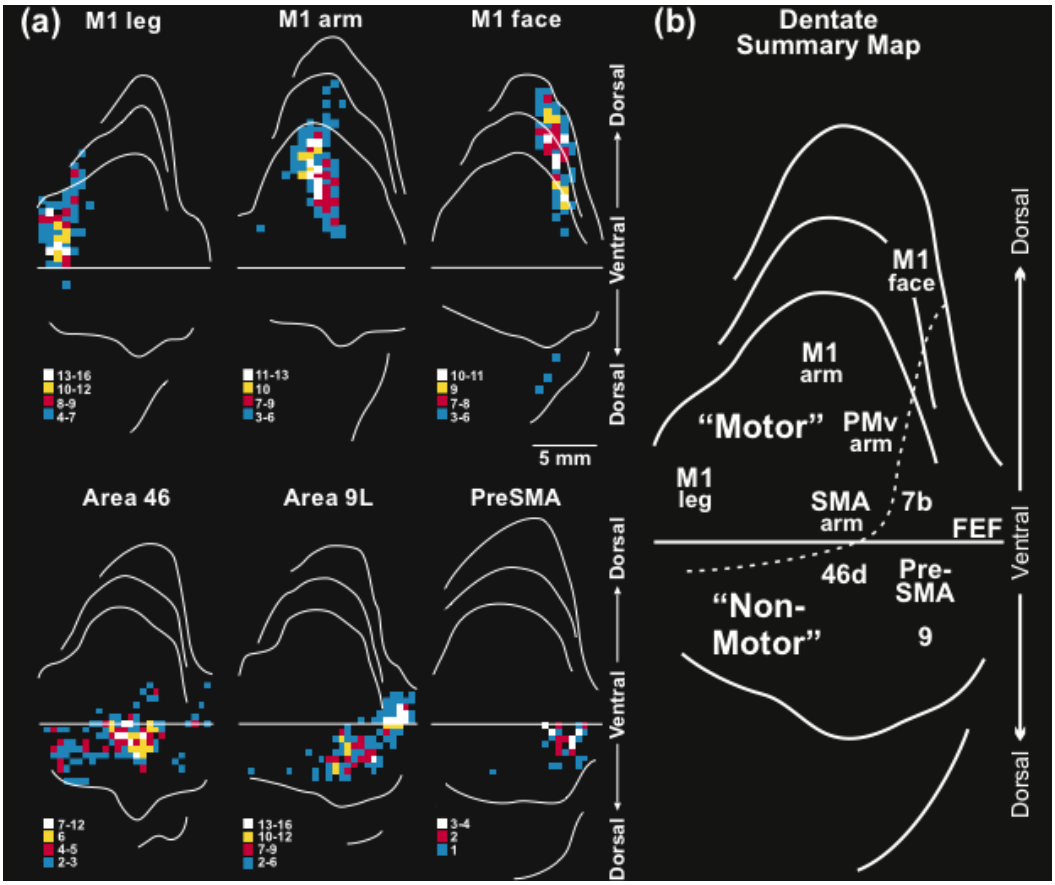


**Figure 1-9: Output channels in the dentate nucleus.**

(a) Top: Dorsal location of output channels to primary motor cortex (M1). Note the somatotopic organization of output channels to leg, arm and face M1. Bottom: Ventral location of output channels to prefrontal cortex. The key below each diagram indicates density of neurons in bins through the nucleus. (b) Summary map of dentate topography. The lettering on the unfolded map indicates the neocortical target of different output channels. The location of different output channels divides the dentate into motor and non-motor domains. Staining for monoclonal antibody 8B3 is most intense in the non-motor domain. The dashed line marks the limits of intense staining for this antibody. The numbers refer to cytoarchitectonic areas. FEF, frontal eye field; M1, face, arm, and leg areas of the primary motor cortex; PMv arm, arm area of the ventral premotor area; PreSMA, presupplementary motor area; SMA arm, arm area of the supplementary motor area. Figure from Bostan et al., 2013.

To date, all the areas of the cerebral cortex that are targets of CB output (M1, premotor areas of the frontal lobe, and selected regions of the PFC and posterior parietal cortex) also have prominent projections to the CB cortex (Glickstein et al., 1985). By contrast, several areas of the

cerebral cortex that lack substantial projections to the CB (areas 46v, 12, and TE) do not appear to be targets of CB output. This observation further implies that cortico-CB networks may be characterized by multiple closed-loops, similar to cortico-BG networks. This possibility has been tested for two areas of the cerebral cortex, M1 and area 46 (Kelly and Strick, 2003). In essence, anterograde transneuronal transport of the H129 strain for herpes simplex virus type 1 was used to determine the regions of CB cortex that receive input fromM1 and the regions that receive input from area 46. Retrograde transneuronal transport of RV was subsequently used to define the regions of the CB cortex that project to M1 and the regions that project to area 46. This approach demonstrated that lobules IV-V, HVIIB, and HVIII both receive input from M1 and project to M1. Similarly, lobule VII (largely hemispheric Crus II, but also vermis) both receives input from area 46 and projects to area 46 (Figure 1-10). These results suggest that the fundamental macro-architectural unit of cortico-CB interactions is a closed-loop circuit.

The obvious spatial separation of the CB regions that are interconnected with M1 and area 46 indicate that the distinct motor and nonmotor domains observed in the dentate nucleus have their counterparts in CB cortex. Specifically, the motor domain includes two regions: one largely in the anterior lobe (lobules III-VI) and another largely in the paramedical lobule and adjacent posterior lobe (HVIIB and HVIII). The nonmotor domain involves regions of the CB cortex located between the areas of motor representation, including portions of the vermis and hemisphere. Considerable support of the separation of CB cortex into motor and nonmotor domains comes from numerous studies (Balsters et al., 2010; Buckner et al., 2011; E et al., 2012; Grodd et al., 2001; Krienen and Buckner, 2009; Manni and Petrosini, 2004; O'Reilly et al., 2010; Ramnani, 2006; Ramnani et al., 2006; Stoodley, 2012; Stoodley and Schmahmann, 2009a; b; 2010; Stoodley et al., 2012).

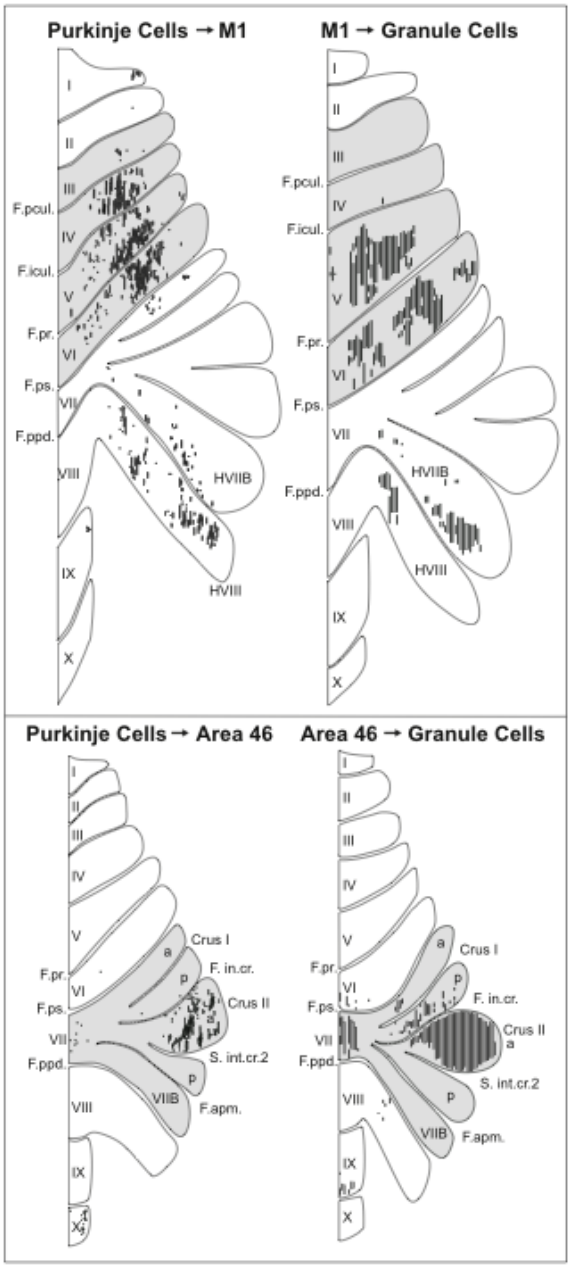


**Figure 1-10: Input-output organization of cerebellar loops with M1 and area 46.**

Top: Organization of cerebellar loops with M1. Left, the distribution of Purkinje cells (small dots) that project to the arm area of M1. These neurons were labeled after retrograde transneuronal transport of rabies from injections into the arm area of M1. Right, the distribution of granule cells (fine lines) that receive input from the arm area of M1. These neurons were labeled after anterograde transneuronal transport of the H129 strain of HSV1 from injections into the arm area of M1. Bottom: Organization of cerebellar loops with area 46. Left, the distribution of Purkinje cells (small dots) that project to area 46. These neurons were labeled after retrograde transneuronal transport of rabies from injections into area 46. Right, the distribution of granule cells (fine lines) that receive input from the area 46. These neurons were labeled after anterograde transneuronal transport of the H129 strain of HSV1 from injections into the area 46. Figure from Bostan et al. 2013.

### 1.3.2 Cerebellar projections to the basal ganglia

The loops that link the CB with the cerebral cortex have traditionally been considered to be anatomically and functionally distinct from those that link the basal ganglia with the cerebral cortex (Doya, 2000; Graybiel, 2005). The outputs from the CB and BG to the cerebral cortex are relayed through distinct thalamic nuclei (Percheron et al., 1996; Sakai et al., 1996). Any interactions between cortico-CB and cortico-BG loops were thought to occur primarily at the neocortical level. Results from recent anatomical experiments using neurotropic viruses challenge this perspective and provide evidence for disynaptic pathways that directly link the CB with the BG (Hoshi et al., 2005).

Briefly, to explore whether the CB projects to the BG, the N2c strain of RV was injected into the sensorimotor territory of the putamen in two cebus monkeys (Hoshi et al., 2005). The survival time was set to allow for two stages of virus transport. Second-order transport of RV from the injection site labeled neurons in the CBN. The neurons in the CBN that were labeled by virus transport were located largely in the dentate nucleus. These results provided evidence that an output stage of CB processing, the dentate, projects via the thalamus to an input stage of BG processing, the putamen.

In another two monkeys, RV was injected into the external segment of the GPe. In these animals, the survival time was set to allow for three stages of transport. Again, most third-order labeled neurons in the CBN were confined to the dentate (Figure 1-11). These results demonstrate that the output from the CB not only influences the striatum, but the target of this influence includes striatal neurons in the indirect pathway that projects to GPe. The injections of RV into GPe involved two different regions of the nucleus. The injection in one animal labeled neurons primarily in ventral and caudal regions of dentate. The injection site in the other animal

was placed approximately 1 mm caudally in GPe and labeled neurons in more dorsal regions of dentate. These observations suggest that the projection from the dentate to the BG is topographically organized.

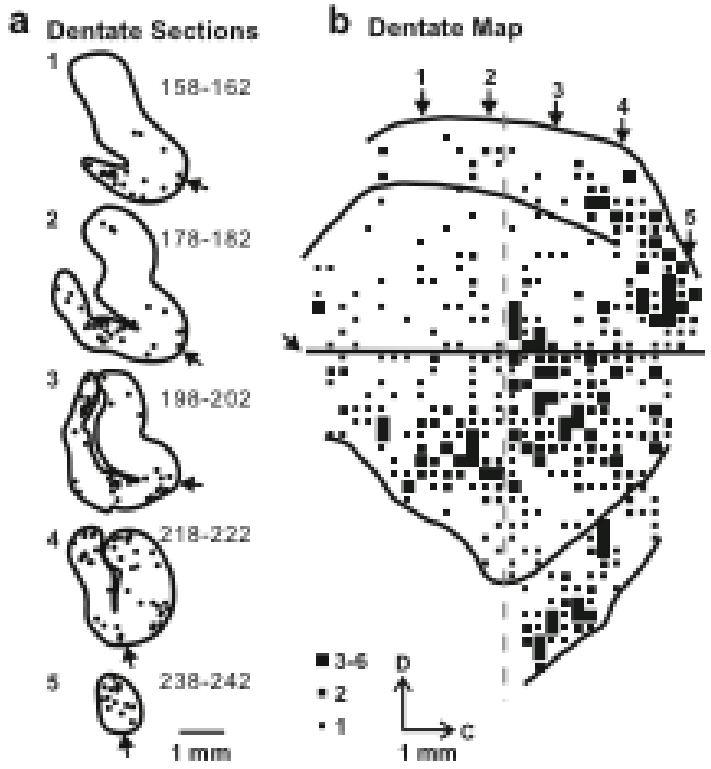


**Figure 1-11: Dentate nucleus projection to the GPe.**

(a) Selected cross-sections of the dentate nucleus. Dots represent the location of third-order neurons labeled by retrograde transneuronal transport of rabies virus from the GPe. Black arrows indicate the level of the horizontal line through the middle of the dentate in (b). (b) Distribution of labeled neurons on an unfolded map of the dentate. The arrows at the top of the map indicate the locations of slices in the left panel. The vertical dashed line marks the rostro-caudal center of the nucleus. Filled squares indicate the density of labeled neurons found in 200 μm × 200 μm bins through the nucleus. Figure from Bostan and Strick, 2012.

As described in the previous section, the dentate is a major source of projections to motor, premotor, prefrontal and parietal areas of cortex (Strick et al., 2009). Based on the topography of these projections, the dentate has been divided into distinct motor and nonmotor domains (Dum et al., 2002). Virus transport from the BG labeled neurons in both the motor and

nonmotor domains of the dentate (Compare Figure 1-11b with 1-9b). These observations indicate that the CB projection to the input stage of BG processing may influence both motor and nonmotor aspects of BG function.

To summarize, studies using transneuronal transport of RV have shown that motor and nonmotor regions of the CB send disynaptic projections to the BG (Hoshi et al., 2005). This novel pathway indicates that these important subcortical centers are more closely linked than previously suspected. One important question that arises from these observations is whether a reciprocal connection exists. Is there a pathway that allows the BG to reach the CB? In Chapter 3, we will describe results from a tracing experiments aimed at addressing this question. Results from these experiments demonstrate that there is a reciprocal connection between the BG and the CB, with important functional implications.

## 1.4 AIMS OF DISSERTATION

The neural connections of the BG have provided important insights into their function. Transneuronal tracing studies have shown that BG output reaches not only M1, but also a wide variety of cerebral cortical areas in the frontal, parietal and temporal lobes (Akkal et al., 2007; Clower et al., 2005; Clower et al., 2001; Hoover and Strick, 1993; Kelly and Strick, 2003; Lynch et al., 1994; Middleton and Strick, 1994; Middleton and Strick, 2001; Prevosto et al., 2010). These results establish concrete pathways that enable BG contributions to both motor and nonmotor functions.

Additionally, transneuronal tracing studies have revealed the macroarchitecture of BG circuits with the cerebral cortex (Kelly and Strick, 2004). These studies have shown that BG

connections with the cerebral cortex are organized as functionally segregated, closed-loop circuits (Kelly and Strick, 2004). Specifically, functionally distinct regions of the cerebral cortex provide inputs to different BG circuits and receive projections from the same BG circuits that they innervate. One notable exception to this pattern has been reported: regions of the striatum that receive limbic (but not motor) input send projections to motor areas in the cerebral cortex, establishing open-loop circuits (Kelly and Strick, 2004; Miyachi et al., 2006; Saga et al., 2011). Consequently, BG circuits with the motor areas of the cerebral cortex can be characterized by both open- and closed-loop macroarchitectures. This finding raises the question of whether the open- and closed-loop circuit organization is unique to BG connections with motor areas of the cerebral cortex.

Finally, transneuronal tracing studies have provided evidence that output from CB can reach the BG disynaptically (Hoshi et al., 2005). This important finding indicates that the two major subcortical systems, the BG and CB, are more closely linked than previously believed. This observation raises the question of whether output from the BG can reach the CB and influence its function.

Overall, the results from studies that use transneuronal tracing techniques to study BG connection bring forth two important questions: 1) Is the open- and closed-loop macroarchitecture unique to BG connections with motor cortical areas? and 2) Does the BG send projections to the CB? Chapters 2 and 3, respectively, will address these questions experimentally.

# 2.0 OPEN- AND CLOSED-LOOP COMPONENTS OF BASAL GANGLIA CIRCUITS WITH THE PREFRONTAL CORTEX

The basal ganglia (BG) participate in multiple, largely segregated, closed-loop circuits with cerebral cortical areas that underlie motor, cognitive, and limbic functions (Alexander et al., 1986). Kelly and Strick (2004) first established that the BG also participate in an open-loop circuit with the primary motor cortex (M1): the ventral striatum (VStr) sends projections to M1, but does not receive input from M1. Here, we used retrograde transneuronal transport of rabies virus (RV) in cebus monkeys to demonstrate that the open- and closed-loop organization of BG circuits with the cerebral cortex extends beyond the motor domain. We injected RV into regions of the dorsal prefrontal cortex (PFC) and set the survival time to allow retrograde transneuronal transport of RV from the injection sites to third-order neurons in the BG. We observed considerable labeling of third-order neurons in striatal regions that are known to receive afferents from the RV injection sites (Calzavara et al., 2007). On the other hand, about 42% of third-order neurons were labeled in regions of the VStr that are not targets of inputs from the PFC, but receive projections from the amygdala (Fudge et al., 2004). These findings demonstrate that the VStr participates in open-loop circuits with regions of the PFC, as well as with motor neocortical areas. These open-loop circuits provide pathways for the limbic BG to influence both cognitive and motor functions.

## 2.1 INTRODUCTION

The basal ganglia (BG) influence motor, cognitive and affective functions through interconnections with the cerebral cortex (Alexander et al., 1986). Cortical areas associated with these different domains project to largely separate regions of the striatum (Calzavara et al., 2007; Künzle, 1975; Selemon and Goldman-Rakic, 1985; Yeterian and Pandya, 1991; 1993; 1998; Yeterian and Van Hoesen, 1978). The topography of cortical inputs establishes functional domains in the striatum that mirror those in the cerebral cortex. Domain specific information is then carried forward through topographically organized BG circuits back to the cerebral cortex, via the thalamus (Parent and Hazrati, 1995a). In both the associative and motor domains, there is evidence that cortical areas providing input to a BG circuit are the targets of output from the same circuit (Kelly and Strick, 2004). Therefore, an important component of the BG connections with the cerebral cortex involves segregated closed-loop connections.

Kelly and Strick (2004) first demonstrated that the BG also participate in an open-loop circuit with the primary motor cortex (M1). They injected rabies virus (RV) into the arm area of M1 and studied the distribution of third-order neurons in the BG (see Figure 2-1 for an illustration of RV transport following injections into the cerebral cortex). The regions of the striatum and subthalamic nucleus (STN) that receive inputs from arm M1 also contained third-order RV neurons, conforming to a closed-loop organization. Additionally, RV injections into arm M1 labeled third-order neurons in a region of the ventral striatum (VStr) not innervated by arm M1, establishing an open-loop circuit. A similar pattern of findings was later demonstrated for BG circuits with the distal forelimb, hindlimb, and orofacial representations in M1 (Miyachi et al., 2006) and with the dorsal premotor cortex (Saga et al., 2011).

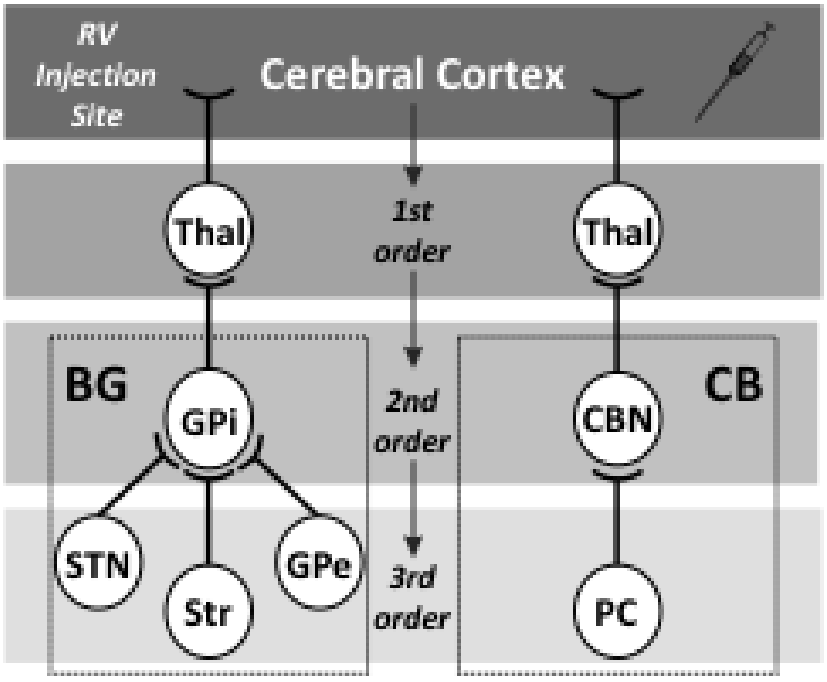


**Figure 2-1: Rabies virus transport through basal ganglia and cerebellar circuits with the cerebral cortex.**

We injected RV into the cerebral cortex. RV is transported retrogradely from the injection sites to first-order neurons that innervate that injection site, including neurons in Thal. The virus then undergoes retrograde transneuronal transport to second-order neurons that innervate the first-order neurons, including neurons in the GPi in the BG and the CBN in the CB. At longer survival times, the virus is transported to third-order neurons that innervate the second order neurons, including neurons in the Str, STN, and GPe in the BG and PC in the CB. Arrows show the direction of RV transport. BG, basal ganglia; CB, cerebellum; CBN, deep cerebellar nuclei; GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; PC, Purkinje cells; RV, rabies virus; STN, subthalamic nucleus; Str, striatum; Thal, thalamus.

Here, we provide evidence that the open- and closed-loop organization of BG circuits with the cerebral cortex extends beyond the motor domain, to associative circuits with regions of the dorsal prefrontal cortex (PFC). We examined the distribution of third-order neurons in the BG following RV injections into the lateral portion of area 9 (9L), the pre-dorsal premotor cortex (PrePMd), or area 46 in the PFC of cebus monkeys. As expected, we observed considerable labeling of third-order neurons in regions of the striatum that are known to receive afferents from the cortical regions injected with RV (Calzavara et al., 2007). Transneuronal transport from 9L, PrePMd and 46 also labeled third-order neurons in regions of the VStr that are not the target of

inputs from these regions, but receive inputs from limbic regions of cerebral cortex, amygdala and hippocampus (Chikama et al., 1997; Ferry et al., 2000; Freedman et al., 2000; Fudge et al., 2005; Fudge et al., 2004; Fudge et al., 2002; Haber et al., 1995; Kunishio and Haber, 1994; Pandya et al., 1981; Russchen et al., 1985). These findings indicate that the VStr participates in open-loop circuits not only with motor areas of the cerebral cortex, but also with the dorsal PFC. These open-loop circuits reveal the potential for the limbic BG to influence both cognitive and motor processing. We quantified the relative contributions of the open-loop component of BG circuits with the cerebral cortex and discuss the possibility that it is topographically organized.

## 2.2 MATERIALS AND METHODS

### 2.2.1 Subjects

This report is based on observations from 8 cebus (Cebus Apella) monkeys (Table 1). In each monkey, we injected a strain of RV into a region of the frontal cortex. In most of our prefrontal cortical injections, we mixed RV with 0.02 % of a conventional tracer (ß subunit of cholera toxin, CTb). This low concentration of CTb does not interfere with RV transmission and facilitates the identification of the injection site and of first order neurons (e.g., neurons in the thalamus and the basal forebrain) (Coffman et al., 2011; Prevosto et al., 2010).

The protocol was approved by the Institutional Animal Care and Use Committee and the Biosafety Committee. Biosafety practices conformed to the Biosafety Level 2 regulations outlined in the Biosafety in Microbiological and Biomedical Laboratories (Department of Health

and Human services publication no. 93-8395). Details of the procedures of handling virus and virus-infected animals conformed to those published previously (Kelly and Strick, 2000).

### 2.2.2 Surgical procedures

All surgical procedures were performed under aseptic conditions. The night before surgery, the monkeys were administered dexamethasone (0.5 mg/kg i.m.). Monkeys were restricted from food the morning of surgery. They were sedated with ketamine (20 mg/kg, i.m.), intubated, and maintained on gas anesthesia (isoflurane, 1.5-3%). Dexamethasone (0.5 mg/kg, i.m.), glycopyrrolate (0.01 mg/kg, i.m.), an antibiotic (ceftriaxone, 75 mg/kg, i.m.) and an analgesic (buprenorphine, 0.02 mg/kg, i.m.) were administered at the time of surgery. Respiration rate, blood oxygen level, body temperature, and sensitivity to noxious stimuli were monitored at regular intervals during the procedures.

### 2.2.3 Virus injections

Each monkey had its head restrained in a Kopf stereotaxic frame (David Kopf Instruments, Tujunga, CA). A large craniotomy was performed over the left frontal cortex and the dura mater was cut and raised to allow access to the areas of interest. We used Hamilton syringes to place multiple injection tracks into the frontal cortex (Table 2-1).

The location of each injection site was based on surface landmarks and their known relationships to the cytoarchitectonic borders of M1 and prefrontal cortex (Barbas and Pandya, 1989; Dum and Strick, 1991; Woolsey et al., 1952). M1 injection sites included the anterior bank of the central sulcus and the surface of the precentral gyrus. Prefrontal cortex injections

were guided by magnetic resonance images acquired before surgery. Needle penetrations were spaced 1 – 1.5 mm apart, except to avoid blood vessels. In most cases, we injected small amounts (0.2 µL) of RV or RV mixed with 0.02% CTb at every 0.5 mm along the depth of each injection track. The injection needle was left in place for 30 seconds to 2 minutes after each deposit of virus. When all injections were complete, the dura mater was repositioned and the incision was covered with bone or a plastic strip and closed. The monkeys were placed in an isolation chamber and administered an analgesic (buprenorphine, 0.01 – 0.02 mg/kg, i.m.) and dexamethasone (0.25 – 0.5 mg/kg, i.m.) every 12 hours for up to 2 days after surgery.

### 2.2.4 Histological procedures

At the end of the survival time, the monkeys were deeply anesthetized using ketamine (25 mg/kg, i.m.) followed by pentobarbital sodium (40 mg/kg, i.p.). They were perfused transcardially with 0.1 M phosphate buffer (pH 7.4), followed by 10% buffered formalin, and then a mixture of 10% buffered formalin and 10% glycerol. The brain was removed and stored in 10% buffered formalin and 10% glycerol overnight and then in 10% buffered formalin and 20% glycerol for 5 – 14 days at 4 ºC.

Blocks of tissue (cerebral cortex, brainstem, and CB) were individually frozen and sectioned at 50 µm. Every 10th section was stained with cresyl violet for cytoarchitecture analysis. Brain sections were immunohistochemically reacted according to the avidin-biotin peroxidase method (Vectastain, Vector Laboratories, Burlingame, CA). Every second or fourth section was reacted with mouse anti-M959 (1:300, supplied by A. Wandeler, Animal Disease Research Institute, Nepean, ON, Canada) to detect RV. In animals where we co-injected CTb, every fourth section was reacted with goat anti-choleragenoid (1:10,000; List Biological

Laboratories, Campbell, CA) to detect CTb. Reacted tissue sections were mounted on gelatin coated glass slides, air dried, and coverslipped.

### 2.2.5 Data analysis

Brain sections through the cerebral cortex were examined for immunostaining using bright field and polarized illumination. Data were plotted using a computerized system (MDPlot 2 or 5, AccuStage, Shoreview, MN) attached to a microscope system (Olympus Bx51). These systems use optical encoders to measure the X-Y movements of the microscope stage and store the coordinates of section outlines and labeled neurons. We digitized the outline of cortical sections, the border between the cerebral cortex and white matter, the BG nuclei and the location of (RV or CTb) labeled neurons.

### 2.2.6 Injection sites

We confirmed the sites of entry of the injection needle on the fixed tissue and on histological sections. In animals where we co-injected CTb we used the CTb labeling to identify and reconstruct the injection sites. We plotted the extent of CTb spread on individual sections and created unfolded maps of the cerebral cortex, using custom laboratory software. To define RV injection sites in animals in which we did not co-inject CTb, we reconstructed each penetration of the injection needle and plotted the distribution of labeled neurons around them, as detailed previously (Kelly and Strick, 2003). All injection sites were then outlined on a representative map of a cebus monkey frontal cortex, similar to Kelly and Strick (2003).

## 2.3 RESULTS

We used RV to study the circuits linking the BG with the frontal cortex in nonhuman primates. RV is transported transneuronally in the retrograde direction in a time-dependent fashion (Figure 2-1) (Kelly and Strick, 2000; Kelly and Strick, 2003; 2004). We injected RV into selected sites within the frontal cortex of cebus monkeys (Figure 2-2) and allowed for different orders of transport of the virus (Table 2-1). We then examined the distribution of labeled neurons in selected BG nuclei and regions of the basal forebrain.

**Table 2-1: Experiments and virus transport.**

| Animal | Injection Site | Virus Strain | Tracks | Total Injections | Total Volume (µL) | Transport Order |
|---|---|---|---|---|---|---|
| **AB11** | PrePMd | N2c + 0.02% CTb | 9 | 36 | 7.2 | 3 |
| **AB12** | Area 9L | N2c + 0.02% CTb | 12 | 48 | 9.6 | 3 |
| **AB13** | PrePMd | N2c + 0.02% CTb | 9 | 36 | 7.2 | 3 |
| **AB15** | Area 9L | N2c-GFP + 0.02% CTb | 8 | 32 | 6.4 | 2 |
| **K10** | Area 46 | CVS-11 | 12 | 48 | 9.6 | 3 |
| **K8** | M1 | CVS-11 | 8 | 22 | 4.4 | 3 |
| **K9** | M1 | CVS-11 | 10 | 25 | 5 | 1 |
| **R26** | M1 | CVS-11 | 9 | 40 | 9 | 2 |

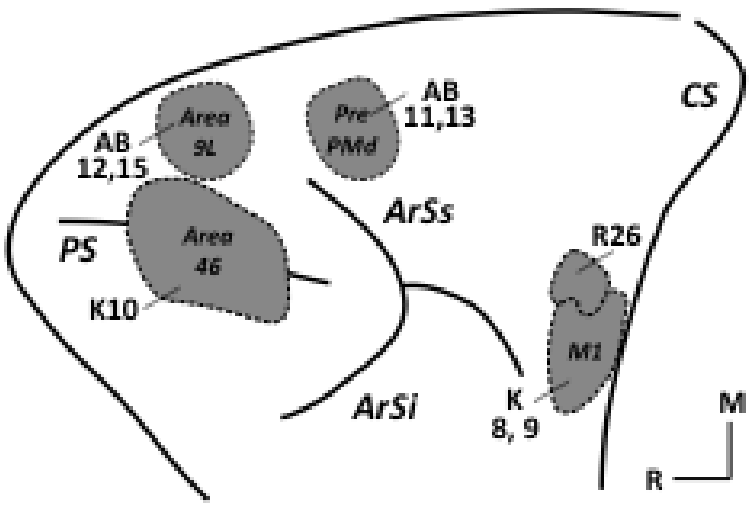


**Figure 2-2: Injection sites.**

Injection sites are outlined on the lateral view of the left hemisphere of the Cebus monkey. ArSi, inferior limb of the arcuate sulcus; ArSs, superior limb of the arcuate sulcus; CS, central sulcus; M, medial; PS, principal sulcus; R, rostral.

### 2.3.1 Third-order neurons labeled in the striatum following rabies virus injections into the dorsal prefrontal cortex

In separate animals, we injected RV into the lateral portion of area 9 (n = 1), PrePMd (n = 2), or area 46 (n = 1) of cebus monkeys (Figure 2-2 and Table 2-1). In these animals, we set the survival time to allow retrograde transneuronal transport of rabies virus from the injection sites to third-order neurons in the striatum and STN (see Figure 2-1 for an illustration of RV transport). The suitability of the survival time was confirmed by the presence of third-order Purkinje cells and absence of any fourth-order granule cells or interneurons labeled in the cerebellar cortex (see (Kelly and Strick, 2003; 2004)).

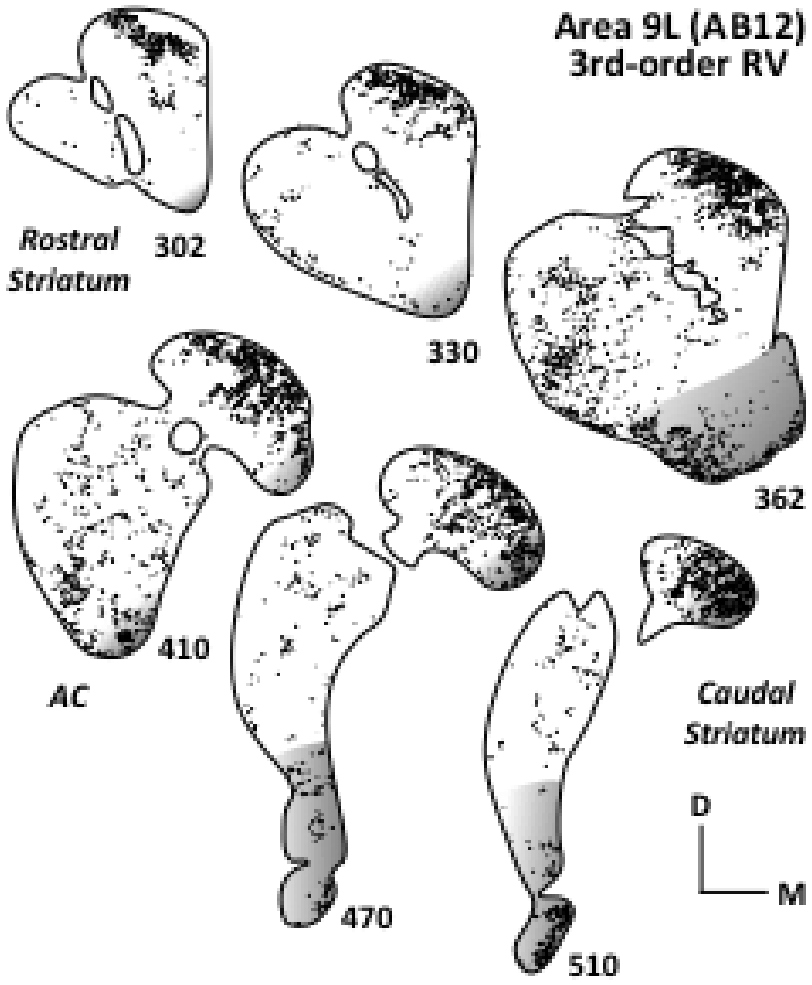


**Figure 2-3: Third-order labeling in the striatum after RV injections into area 9L.**

Different sections throughout the striatum of monkey AB12, with RV labeled neurons (black dots) after RV injections into Area 9L. Numbers represent section numbers. Shaded region represents the ventral striatum. AC, anterior commisure; D, dorsal; M, medial; RV, rabies virus.

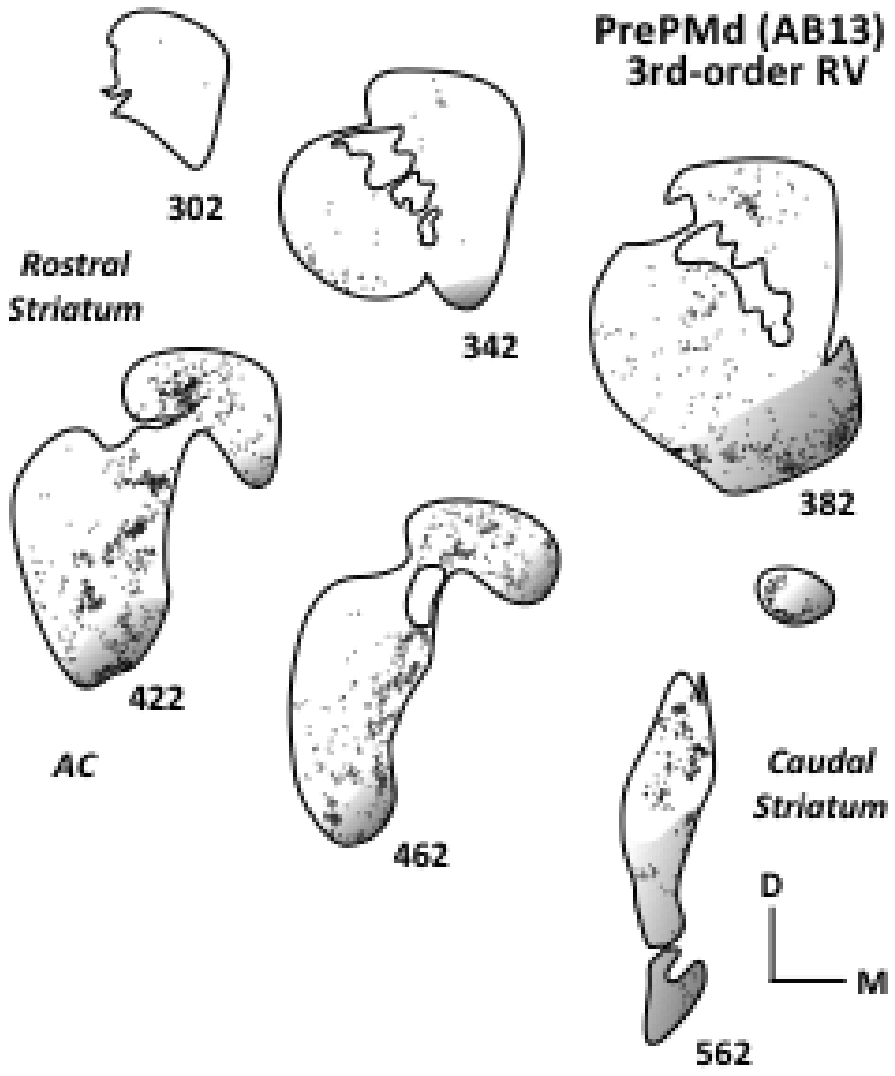


**Figure 2-4: Third-order labeling in the striatum after RV injections into PrePMd.**

Different sections throughout the striatum of monkey AB13, with RV labeled neurons (black dots) after RV injections into PrePMd. Numbers represent section numbers. Shaded region represents the ventral striatum. AC, anterior commisure; PrePMd, pre-dorsal premotor cortex; D, dorsal; M, medial; RV, rabies virus.

After injections into area 9L, PrePMd, or area 46, substantial numbers of third-order neurons were observed in the same regions of the striatum that receive afferents from the same area of the cerebral cortex (Calzavara et al., 2007; Selemon and Goldman-Rakic, 1985; Yeterian and Pandya, 1991).

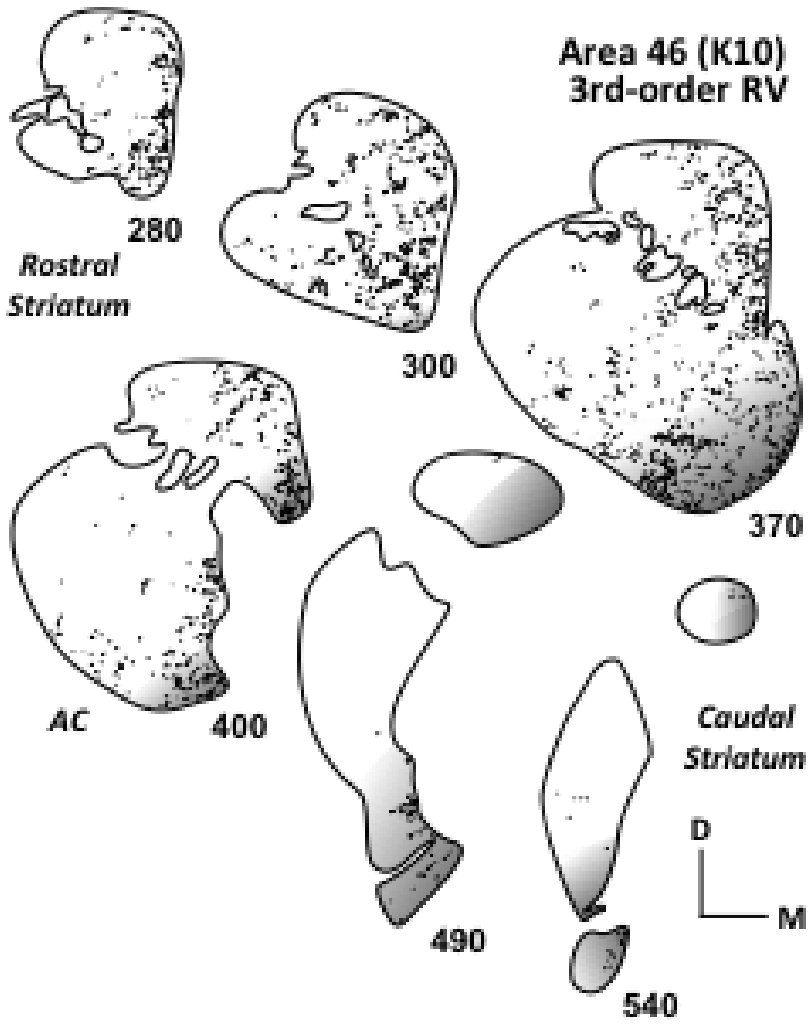


**Figure 2-5: Third-order labeling in the striatum after RV injections into area 46.**

Different sections throughout the striatum of monkey K10, with RV labeled neurons (black dots) after RV injections into Area 46. Numbers represent section numbers. Shaded region represents the ventral striatum. AC, anterior commisure; D, dorsal; M, medial; RV, rabies virus.

First, transneuronal transport of RV from 9L labeled third-order neurons in the medial and dorsal aspects of the caudate nucleus (Figure 2-3). Second, transneuronal transport of RV from PrePMd labeled third-order neurons more laterally within the caudate nucleus (Figure 2-4). Finally, transneuronal transport of RV from area 46 labeled third-order neurons in central regions of the caudate, ventral to those labeled by RV injections into 9L (Figure 2-5). Overall, the topographical arrangement of third-order neurons labeled after RV injections into 9L, PrePMd,

and area 46 closely resembles the organization of projections from the same neocortical areas to the caudate nucleus (Calzavara et al., 2007; Selemon and Goldman-Rakic, 1985; Yeterian and Pandya, 1991). This correspondence occurs despite the fact that the injection sites in our study do not precisely match those from previous studies of cortico-striatal projections and have been performed in a different species of monkey (cebus vs. macaque monkeys). These results suggest that the different regions of the dorsal PFC (9L, PrePMd, and area 46) participate in separate closed-loop circuits with the striatum.

Transneuronal transport from each RV injection into the dorsal PFC also labeled third-order neurons outside of the striatal region that is the target of inputs from the injection site. In particular, we observed numerous neurons labeled in regions of the VStr (Figures 2-3, 2-4, 2-5, shaded areas). The VStr refers to the limbic-related portion of the striatum and can be best identified by the extent of the striatum that receives amygdala inputs (Fudge et al., 2004). The VStr receives not only amygdala inputs (Fudge et al., 2004; Fudge et al., 2002; Russchen et al., 1985), but also topographically organized projections from cerebral cortical areas that are closely associated with the amygdala and limbic function, including areas in the medial and orbital PFC, the cingulate cortex, the insular cortex, and the anterior temporal cortex (Chikama et al., 1997; Ferry et al., 2000; Freedman et al., 2000; Haber et al., 1995; Kunishio and Haber, 1994; Pandya et al., 1981; Van Hoesen et al., 1981; Yeterian and Van Hoesen, 1978). Importantly, the VStr does not receive any inputs from the dorsal PFC (Calzavara et al., 2007; Yeterian and Pandya, 1991). Therefore, area 9L, the PrePMd, and area 46 receive inputs from a striatal region that is not the target of their cortico-striatal afferents. Consequently, each of these regions in the dorsal PFC participates in an open-loop circuit with the VStr.

### 2.3.2 The open-loop circuits between the ventral striatum and the cerebral cortex

We evaluated the correspondence between the VStr and the open-loop component of cortico-BG circuits, by comparing the striatal regions that are known to receive amygdala projections with that of third-order neurons labeled after RV injections into the different areas of the frontal cortex. For example, after RV injections into area 9L, large numbers of third-order neurons were located in regions of the VStr (Figure 2-6, shaded region in middle panel) that do not receive input from 9L (Figure 2-6, left panel, from Calzavara et al. 2007) but are known to receive amygdala input (Figure 2-6, right panel, from Fudge et al. 2004). Similar comparisons of the location of third-order striatal labeling (Figures 2-4 and 2-5) with the regions of amygdala receiving striatum (from Fudge et al., 2004) indicates that the VStr also participates in open-loop circuits with the PrePMd and area 46. Therefore, the VStr participates in open-loop circuits with several regions of the dorsal PFC, as well as with motor areas of the cerebral cortex (Kelly and Strick, 2004; Miyachi et al., 2006; Saga et al., 2011). To estimate the strength of these open-loop circuits we approximated the extent of the VStr, based on the striatal regions that receive amygdala efferents (from Fudge et al., 2004). This definition of the VStr includes the shell and core of the nucleus accumbens (NAcc), as well as more caudal regions of the VStr and the lateral amygdalostriatal area (see Figure 2-6, right panel). We estimate that approximately 42% of third-order neurons in the striatum are located within the VStr (Table 2-2), not only after RV injections into the dorsal PFC (n = 4), but also after injections into M1 (n = 1).

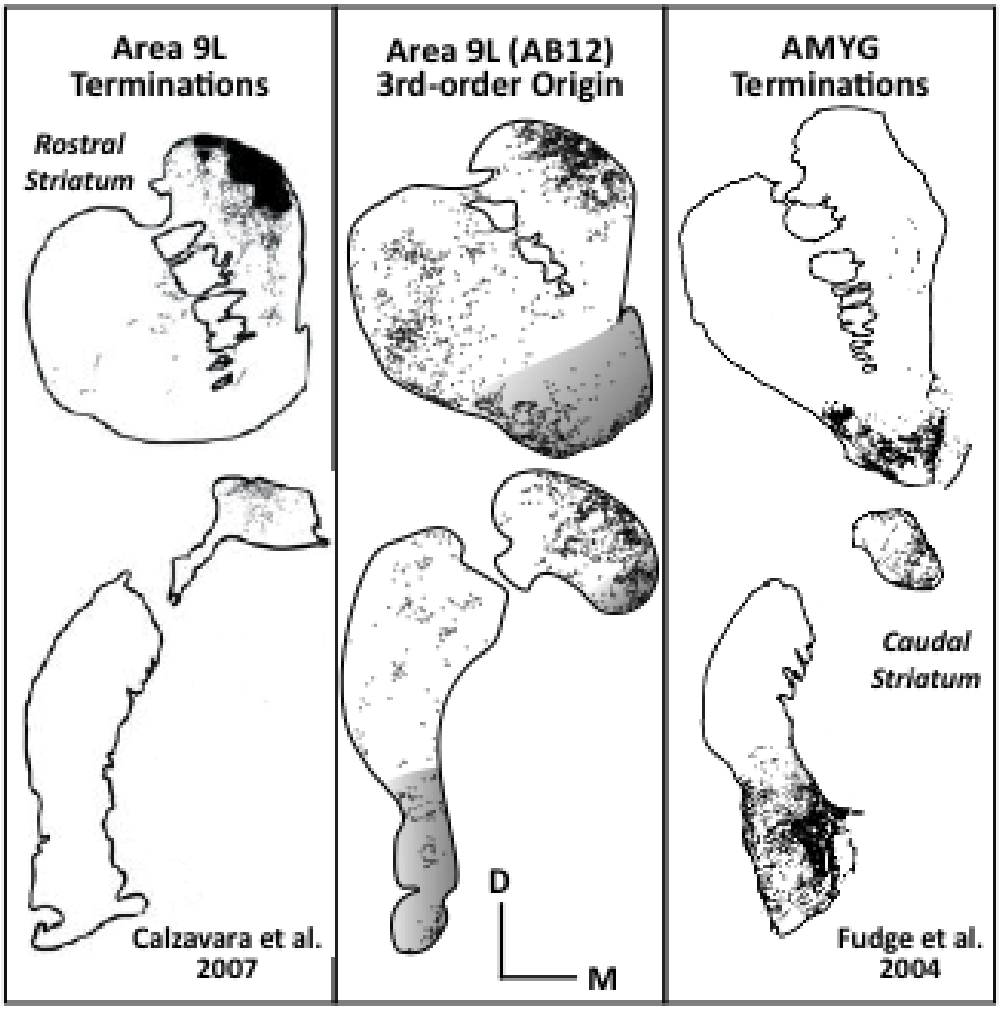


**Figure 2-6: Open-loop projection from the ventral striatum to 9L.**

Each column shows results from different experiments on two representative striatal sections, at similar rostro-caudal levels in all the experiments. Right: Anterogradely labeled terminals after tracer injections into 9L, from Calzavara et al., 2007. Center: RV labeled third-order cells after RV injections into 9L, from the current study. Left: Anterogradely labeled terminals after injection into the basal nucleus, magnocellular subdivision, of the amygdala, from Fudge et al., 2004. Shaded region in the middle panel outlines the ventral striatum, as identified by the amygdala projection to the striatum (left panel). Note that there are no terminals labeled in the corresponding region in the right panel. This is indicative of an open-loop projection from ventral striatum to area 9L. AMYG, amygdala; D, dorsal, M, medial.

**Table 2-2: Third-order RV neuron distribution in the striatum after injections into the frontal cortex.**

| Animal | Injection Site | 3rd order RV neurons labeled in the striatum | | % cells in the VStr |
|---|---|---|---|---|
| | | Total | VStr | |
| **AB11** | PrePMd | 13188 | 6948 | 53 |
| **AB13** | PrePMd | 16669 | 6848 | 41 |
| **AB12** | Area 9L | 47353 | 18415 | 39 |
| **K10** | Area 46 | 14755 | 5769 | 39 |
| **K8** | M1 | 13745 | 5435 | 40 |

### 2.3.3 The pathway from the ventral striatum to the dorsal prefrontal cortex and to motor areas of the cerebral cortex

The precise route from the VStr to the dorsal PFC and M1 remains unclear. We compared the location of second-order neurons labeled in the GPi and the SNpr with the known location of VStr afferents to these structures (Haber et al., 1990). Confirming previous findings (Hoover and Strick, 1999; Middleton and Strick, 2000b; Middleton and Strick, 2002), RV injections into area 9L label second-order neurons in dorso-medial regions of the GPi and in lateral regions of the SNpr. Second-order neurons labeled by RV injections into M1 were confined to the center of the GPi, rostro-caudally. However, the VStr does not project to any of these locations in the GPi or SNpr (Haber et al., 1990). Therefore, retrograde transneuronal transport of RV cannot reach the third-order neurons in the VStr via a relay in the GPi or SNpr.

Alternatively, third-order labelling in the VStr following RV injections into the dorsal PFC and M1 could be mediated through a different efferent pathway from the VStr. Unlike dorsal regions of the striatum that send projections exclusively to nuclei within the BG, the VStr has also been shown to send projections to the nucleus basalis of Meynert (NBM) in the basal forebrain, the lateral hypothalamus, and the medial thalamus (Haber et al., 1990). We observe

second-order RV labeled neurons in the NBM after RV injections into both M1 and regions of the dorsal PFC (Figure 2-7). These neurons are labeled in regions of the basal forebrain that have been shown to receive inputs from the VStr (Haber et al., 1990). Neurons of the NBM are known to send direct projections to the cerebral cortex (Mesulam et al., 1983). Correspondingly, we also observe first-order neurons labeled in the NBM after injections into both M1 and regions of the dorsal PFC (Figure 2-7).

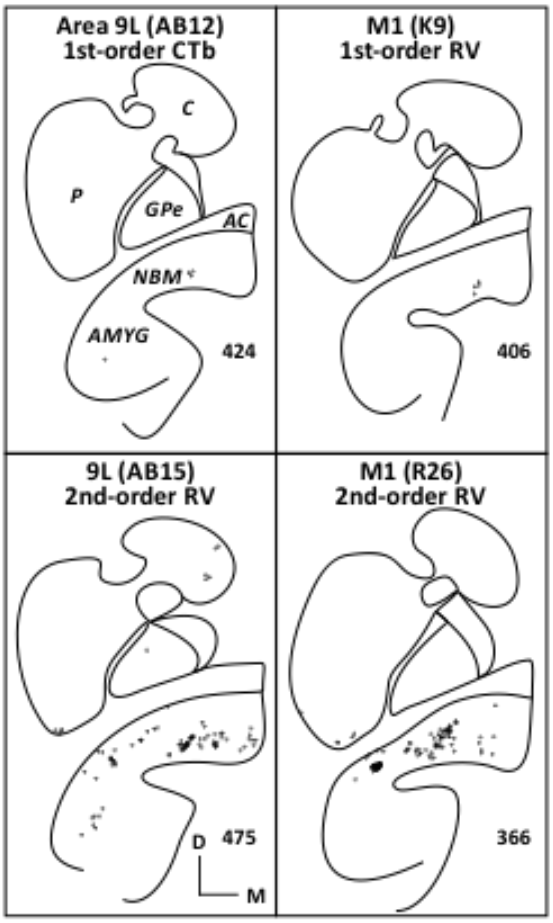


**Figure 2-7: First- and second-order labeling in the NBM after injections into area 9L and M1.**

Left, top: First-order CTb labeled neurons (black dots) after injections of RV and 0.02% CTb into 9L in monkey AB12. Left, bottom: Second-order RV labeled neurons (black dots) after injections of RV into 9L in monkey AB15. Right, top: First-order RV labeled neurons (black dots) after injections of RV into M1 in monkey K9. Right, bottom: Second-order RV labeled neurons (black dots) after injections of RV into M1 in monkey R26. Section number shown under each section. AMYG, amydala; C, caudate; CTb, ß subunit of cholera toxin; D, dorsal; GPe, external segment of the globus pallidus; M, medial; NBM, nucleus basalis of Meynert; P, putamen.

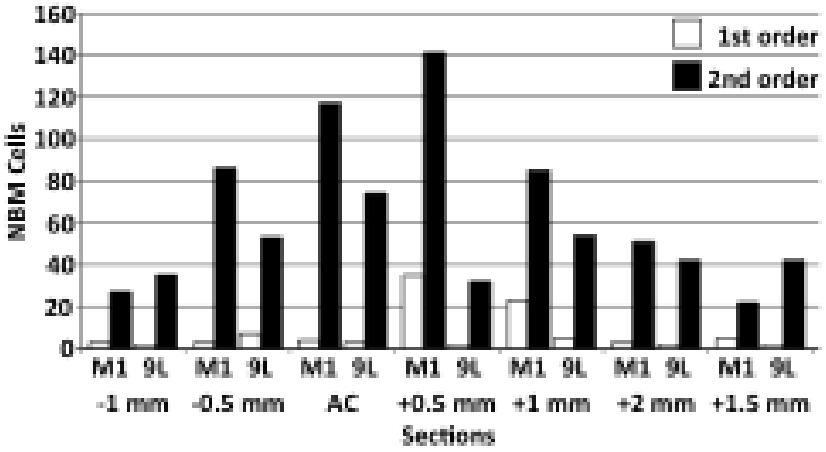


**Figure 2-8: Rostro-caudal distribution of first- and second-order NBM neurons after injections into area 9L and M1.**

Histogram of the rostro-caudal distribution of first- and second-order neurons in the NBM after injections into area 9L and M1. White columns represent first-order neuron counts, while black columns represent second-order neurons counts. Numbers of neurons are shown for representative sections; approximate distance from the AC is shown under each set of sections. NBM, nucleus basalis of Meynert; AC, anterior commisure.

The neurons labeled in the NBM in our second-order experiments are considerably more numerous than those labeled in first-order experiments (Figure 2-8) and are located in more widespread regions of the NBM (Figure 2-7). We observe limited, if any, striatal labeling in our second-order experiments (Figure 2-7). Therefore, it is unlikely that the VStr projections reach NBM neurons that project directly to the cerebral cortex. Third-order RV labeled neurons in the VStr after RV injections into motor regions of the cerebral cortex and regions of the dorsal PFC are most likely labeled through a relay in the NBM.

### 2.3.4 Topographical organization of the open-loop circuit

The organization of open-loop circuits between the BG and cerebral cortex appears to be quite different from that of the closed-loop circuits. The closed-loops are topographically organized. For instance, third-order neurons labeled after RV injections into area 9L or the PrePMd are segregated in the caudate nucleus, with the highest density of neurons projecting to 9L being located medial to those projecting to the PrePMd (Figure 2-9).

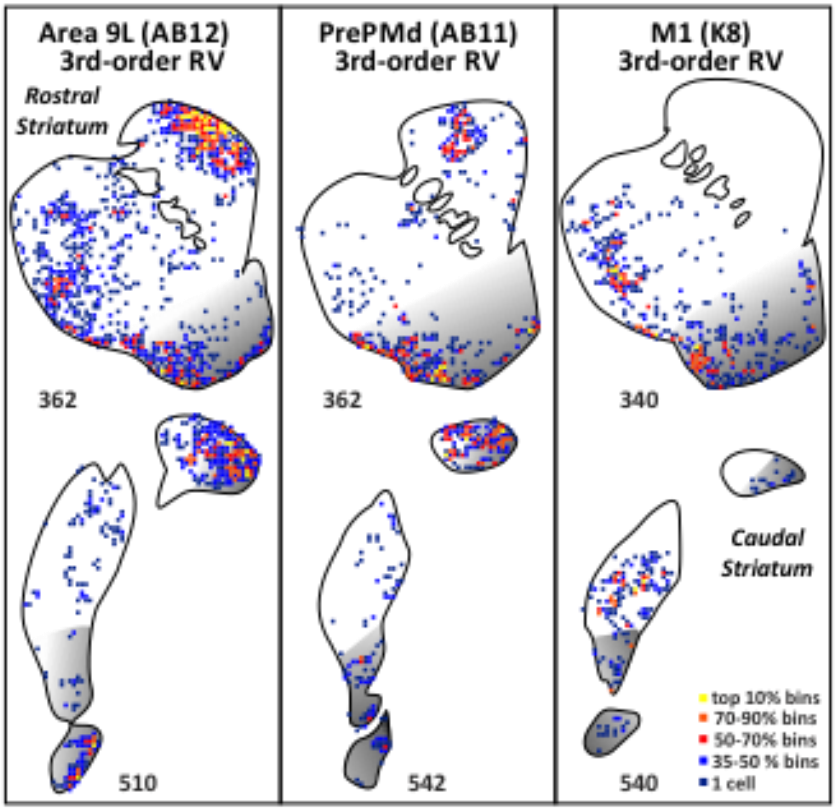


**Figure 2-9: Density of third-order neurons labeled after RV injections into area 9L, PrePMd and M1.**

Location and density of neurons labeled in the striatum following retrograde traneneuronal transport of RV from 9L, PrePMd, and M1. In each case (column), two representative striatal sections, at similar rostro-caudal are shown. Indiviual section numbers are indicated. Shaded regions represent the outline of the ventral striatum. The density of labeled neurons was determined by counting the number of labeled cells within 200 µm bins in each section. The number of cells per bin was divided into five levels and color coded: yellow, to 10% bins (90-100%); orange, 70-90%; red, 50-70%; blue, 35-50%; dark blue shows once cell per bin. M1, primary motor cortex; Pre-PMd, pre-dorsal premotor cortex; RV, rabies virus.

In contrast, we observed a high degree of overlap in the third-order neurons labeled in the VStr after RV injections regions into M1 and areas of the dorsal PFC (Figure 2-9). To better illustrate this point, we overlapped sections through the rostral striatum (from the top panel in Figure 9) that show the density of third-order neurons labeled after RV injections into 9L, PrePMd and M1 (Figure 2-10). Regions in the caudate nucleus that project to the PrePMd are distinct (more central and medial) from those that project to 9L. Similarly, there is a distinction between the less dense projection regions to 9L and M1 in the dorsal putamen. However, in the VStr (shaded region in Figure 2-10), third-order neurons labeled after RV injections into 9L and PrePMd are intermingled with each other, as well as with third-order neurons labeled after RV injections into M1. Some of this overlap may be a consequence of the overlap observed in the first- and second-order labeling in the NBM following injections into areas of the dorsal PFC and M1 (Figure 2-7). Overall, these results suggest that the open-loop circuits involving the frontal cortex are intermingled and non-specific.

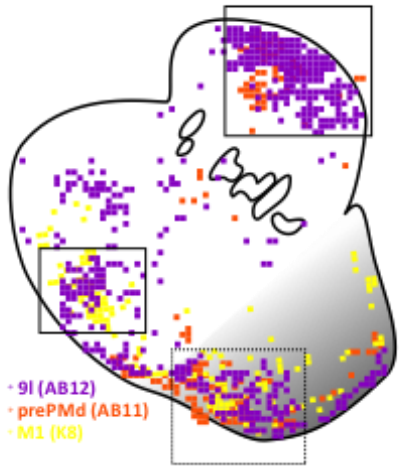


**Figure 2-10: Topography of the open- and closed-loop striatal projections to the frontal cortex.**

Rostral striatal sections from Figure 2-9 have been scaled and overlapped to show peak densities (more than 3 cells per bin) of neurons labeled following RV injections into 9L (purple), PrePMd (orange) and M1 (yellow). Shaded region represents the outline of the ventral striatum. Solid-line rectangles outline regions that are topographically organized in the caudate the dorsal putamen. The dotted-line rectangle outlines a region in the ventral striatum without clear topography. M1, primary motor cortex; Pre-PMd, pre-dorsal premotor cortex.

## 2.4 DISCUSSION

Previous work has shown that BG connections with motor cortical areas are organized as open- and closed-loop circuits (Kelly and Strick, 2004; Miyachi et al., 2006; Saga et al., 2011). Using the retrograde transneuronal transport of RV, we extended these findings beyond the motor domain. We provided evidence that BG connections with the dorsal PFC are organized as open- and closed-loops circuits. Specifically, regions of the striatum that receive inputs from areas 9L, PrePMd and 46 in the dorsal PFC send projections back to the same cerebral cortical areas, forming closed-loop circuits. Regions of the VStr do not receive inputs from areas 9L, PrePMd, or 46 in the dorsal PFC, but send projections to all of these cerebral cortical areas, establishing open-loop circuits. Furthermore, we found that the open-loop component is significant and originates in similar regions throughout the VStr, to reach both associative and motor areas of the cerebral cortex. Overall, our results describe a substantial pathway for limbic processing in the BG to influence both cognitive and motor functions of the cerebral cortex. These results indicate that our current conceptualization of BG connections with the cerebral cortex needs to be updated to include both close-loop parallel processing pathways and open-loop pathways that enable modulation of the associative and motor loops by the limbic system.

Currently, the prevalent view of BG circuits with the cerebral cortex is that they are organized as parallel pathways subserving motor, associative, and limbic functions (Alexander et al., 1986). Several notable findings have helped establish this view. First, cortical areas associated with motor, associative, and limbic domains send projections to largely distinct areas of the striatum (Calzavara et al., 2007; Haber et al., 1995; Kunishio and Haber, 1994; Künzle, 1975; Selemon and Goldman-Rakic, 1985; Yeterian and Pandya, 1991; Yeterian and Van Hoesen, 1978). Second, distinct functional domains of the striatum are interconnected with

corresponding domains within other BG nuclei (Parent and Hazrati, 1995a). Finally, separate output channels from the major output nuclei of the BG reach distinct functional domains in the cerebral cortex (Kelly and Strick, 2004; Middleton and Strick, 2000b). The emergent perspective of parallel pathways linking the BG with functionally diverse regions of the cerebral cortex provides an anatomical basis for BG contributions to multiple aspects of behavior (Middleton and Strick, 2000b). However, this perspective does not account for interactions between the functionally distinct pathways.

Others have proposed mechanisms for means by which BG circuits with different cerebral cortical regions can influence each other (for a review, see Haber, 2003). Of these, the mechanism that has received the most attention is based on studies in rodents that point to the NAcc as an interface between the limbic and motor systems (Haber et al., 2000). Briefly, these studies provide evidence that the NAcc sends projections to neurons in the SN, some of which target the dorsal striatum (Nauta et al., 1978; Somogyi et al., 1981). In the primate, a direct link between the limbic striatum and the motor striatum via the SN is unlikely (Haber et al., 2000), as the connections between the striatum and dopaminergic cells in the SN are reciprocal and topographically organized: the ventral tegmental area and medial SN are interconnected with the VStr, the lateral and ventral SN are interconnected with the associative and motor striatum (Lynd-Balta and Haber, 1994). However, the projection from the VStr to the midbrain extends beyond the region that it is reciprocally connected with, into regions that project to the associative striatum (Haber et al., 2000). Therefore, it has been proposed that the VStr may influence regions of the SN that send dopaminergic projections to the associative striatum. Similarly, the associative striatum may influence regions of the SN that send dopaminergic projections to the sensorimotor striatum (Haber, 2003; Haber et al., 2000). The hypothesis is that

striatal projection to the SN may facilitate information transfer in adjacent nigro-striatal circuits, by inhibiting GABAergic interneurons, or pars reticulata cells, and disinhibiting dopaminergic projections to the striatum. There are several issues with this hypothesis. First, in the primate, there is no synaptic evidence for connections between functionally distinct regions of the striatum through dopaminergic cells. There is also no evidence that the striatum projects to GABA interneurons in the SN that synapse onto dopaminergic cells that then target a functionally distinct region of the striatum. Second, the kind of influence that limbic processing would have over associative and then motor striatum through the long chain of spiral connections, mediated by complex dopaminergic effects, remains unclear. Further work is needed to provide physical evidence for these series of synaptic connections and to reveal their extent and any functional significance.

Results from the current study, along with previous findings (Kelly and Strick, 2004; Miyachi et al., 2006; Saga et al., 2011), offer the anatomical substrate for an alternative mechanism by which the VStr can influence both associative and motor processing in BG with the cerebral cortex. These results show that associative and motor regions of the cerebral cortex receive inputs from the VStr through the same number of synapses through which they receive inputs from the associative and motor striatum, respectively. Furthermore, our results indicate that VStr inputs to these cerebral cortical areas are likely to have a consequential impact, since an average of 42% of striatal neurons that project multisynaptically to associative and motor cortical areas originate in the VStr (Table 2-2).

An important question that arises from our findings is how the VStr gains access to the dorsal PFC and motor areas of the cerebral cortex. The VStr projects primarily to the rostral ventral pallidum and parts of SN (Haber et al., 1990; Hedreen and DeLong, 1991; Parent and

Hazrati, 1995a), but not to regions that have prominent outputs to dorsal PFC or the motor areas of the cerebral cortex (Hoover and Strick, 1999; Middleton and Strick, 2000b). Therefore, the projections from the VStr to the dorsal PFC and to motor areas of the cerebral cortex are not mediated by the traditional BG-thalamo-cortical routes. Unlike other striatal regions, the VStr has projections to a limited set of regions outside of the BG, including the NBM (Haber et al., 1990). The projection to the NBM is of particular interest because after injections of RV into M1 and dorsal PFC, we observe dense labeling of second-order neurons in the NBM (Figures 2-7 and 2-8). Therefore, the NBM is a potential intermediate step in the projections from the VStr to M1 and the dorsal PFC.

The NBM contains the Ch4 neuron complex that provides the major source of cholinergic afferents to the cerebral cortex and the amygdala (Johnston et al., 1979; Mesulam et al., 1983; Mesulam and Van Hoesen, 1976; Pearson et al., 1983). If VStr neurons synapsed onto NBM neurons that send direct projections to our injection sites in the cerebral cortex, we would expect to see second-order neurons labeled in the VStr after RV injections into regions of the cerebral cortex. However, in our second-order experiments, we mainly observe an expansion of labeling in the NBM compared to first-order experiments (Figure 2-8) and very few, if any, cells labeled in the striatum (Figure 2-7). This indicates that VStr targets NBM projection neurons to M1 and the dorsal PFC only indirectly. Curently, it is unknown which NMB neurons receive VStr inputs in the primate. Studies in the rat indicate that VStr may target both cholinergic and non-cholinergic cells in the NBM (Bolam et al., 1986b; Grove et al., 1986; Martínez-Murillo et al., 1988; Záborszky and Cullinan, 1992). The characteristics, distribution, and eventual cortical targets of NBM neurons that receive inputs from the VStr remain unclear, even in the rat. Further research is needed to characterize the connection from the VStr to the NBM in the

primate and provide more insights into the path that the VStr takes to reach associative and motor areas of the cortex. What is clear from our results is that both prefrontal and motor areas of the cerebral cortex receive synaptic inputs from the VStr. Future studies using dual-labeled virus tracers will be needed to establish whether individual VStr cells send outputs to one or multiple cortical areas, within or across motor and non-motor domains.

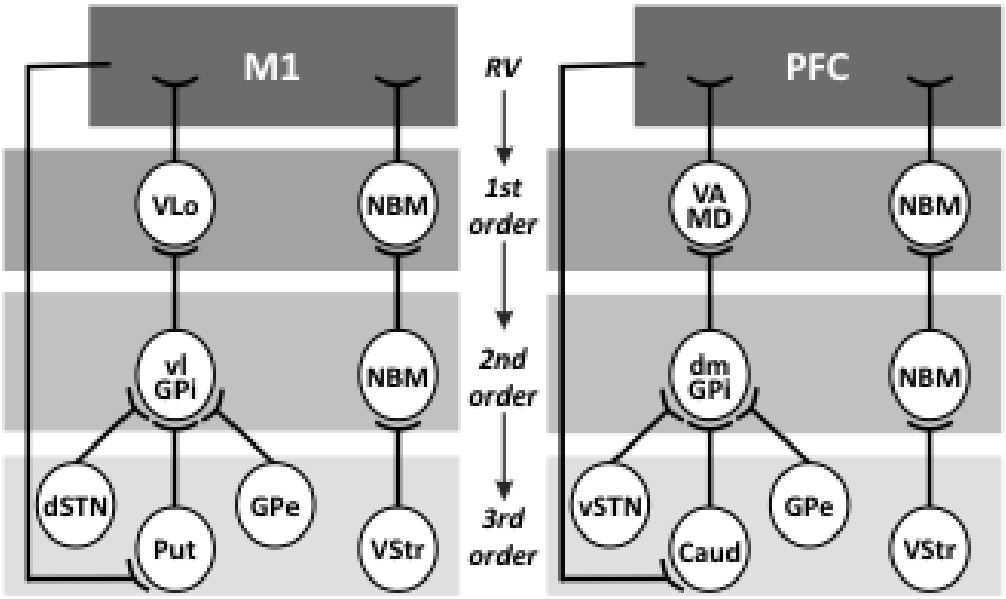


**Figure 2-11: Summary diagram of open- and closed-loop circuits between the basal ganglia and regions of the frontal cortex.**

Circuits with M1 are shown on the left. Circuits with the dorsal PFC are shown on the right. For each region, the closed-loop is shown on the left, while the proposed open-loop through the NBM is shown on the right. Caud, caudate; d, dorsal; dm, dorso-medial; GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; MD, medial dorsal nucleus of the thalamus; NBM, nucleus basalis of Meynert; Put: putamen; STN: subthalamic nucleus; v, ventral; VA, ventral anterior nucleus of the thalamus; vl, ventro-lateral; VLo, ventralis lateralis pars oralis nucleus of the thalamus.

The inputs from the VStr to the dorsal PFC and motor areas of the cerebral cortex are most likely mediated through the NBM (Figure 2-11). Given that the projections from the NBM target the entire cerebral cortex (Mesulam et al., 1983), we suggest that the VStr may reach a much wider range of areas than studied here. If this hypothesis is confirmed, the open-loop

connection between the VStr and the cerebral cortex is likely to have important functional consequences, as the cholinergic innervation of the cerebral cortex by the NBM plays a central role in the neural modulation of attention, arousal, and memory (Mesulam, 2004). Furthermore, the cholinergic projection from the NBM to the cerebral cortex is compromised in a variety of disorders including Alzheimer's disease (Mesulam, 2012), schizophrenia (Heimer, 2000; Hyde and Crook, 2001), and Parkinson's disease (Bohnen and Albin, 2011). If the open-loop component of cortico-BG circuits is indeed mediated by the NBM, it is likely to have important clinical consequences for all of these disorders.

## 3.0 THE BASAL GANGLIA COMMUNICATE WITH THE CEREBELLUM

The basal ganglia (BG) and cerebellum (CB) are major subcortical structures that influence not only movement, but also cognition and affect. Both structures receive input from and send output to the cerebral cortex. Thus, the BG and CB form multisynaptic loops with the cerebral cortex. BG and CB loops have been assumed to be anatomically separate and to perform distinct functional operations. We investigated whether there is any direct route for BG output to influence CB function that is independent of the cerebral cortex. We injected rabies virus into selected regions of the CB cortex in cebus monkeys and used retrograde transneuronal transport of the virus to determine the origin of multisynaptic inputs to the injection sites. We found that the subthalamic nucleus (STN) of the BG has a substantial disynaptic projection to the CB cortex. This pathway provides a means for both normal and abnormal signals from the BG to influence CB function. Previous work has demonstrated that the dentate nucleus of the CB has a disynaptic projection to an input stage of BG processing, the striatum (Hoshi et al., 2005). Taken together these results provide the anatomical substrate for substantial two-way communication between the BG and CB. Thus, the two subcortical structures may be linked together to form an integrated functional network.

## 3.1 INTRODUCTION

The basal ganglia (BG) and cerebellum (CB) are major subcortical structures that influence not only movement, but putatively also cognition and affect (Alexander et al., 1986; Strick et al., 2009). Both structures receive input from and send output to the cerebral cortex. Thus, the BG and CB form multisynaptic loops with the cerebral cortex. The major interactions between these loops were thought to occur largely at the cortical level (Percheron et al., 1996).

Recently, it has been shown that one of the output nuclei of the CB, the dentate nucleus, has a disynaptic projection to an input stage of BG processing, the striatum (Hoshi et al., 2005). This pathway enables CB output to influence BG function. Here, we investigated whether a comparable pathway allows BG output to influence CB function. We injected rabies virus (RV) into regions of the CB cortex in cebus monkeys and used retrograde transneuronal transport of the virus to determine the origin of multisynaptic inputs to the injection sites. Our results indicate that the subthalamic nucleus (STN) of the BG has substantial disynaptic projections to the CB cortex.

## 3.2 MATERIALS AND METHODS

### 3.2.1 Subjects

This report is based on observations from three cebus monkeys (Cebus apella, 1.9–2.6 kg, 2 males and 1 female; Table 3-1). In each monkey, a mixture of the N2c strain of the RV and a

conventional tracer (β subunit of cholera toxin (CTb)) was injected into the cortex of the CB hemisphere.

The protocol was approved by the Institutional Animal Care and Use Committee and the Biosafety Committee. Biosafety practices conformed to the biosafety level 2 regulations outlined in Biosafety in Microbiological and Biomedical Laboratories (Department of Health and Human Services publication no. 93–8395). Details of the procedures for handling virus and virus-infected animals have been published previously (Kelly and Strick, 2000).

### 3.2.2 Surgical procedures

All surgical procedures were performed under aseptic conditions. The night before the virus injection surgery, the monkeys were administered dexamethasone (0.5 mg/kg, i.m.). Monkeys were sedated with ketamine (20 mg/kg, i.m.), intubated, and maintained on gas anesthesia (enflurane; 1.5–2.5%). Dexamethasone (0.5mg/kg, i.m.), glycopyrrolate (0.01 mg/kg, i.m.), and an antibiotic (ceftriaxone; 75 mg/kg, i.m.) were administered at the time of surgery. Respiratory rate, blood oxygen level, body temperature, and sensitivity to noxious stimuli were monitored at regular intervals during the procedure.

### 3.2.3 Virus injections

Each monkey had its head restrained in a Kopf stereotaxic frame (Kopf Instruments). A craniotomy was performed to expose the ventral portions of the occipital cortex and the lateral portion of the posterior CB. With the aid of a surgical microscope, we used a Hamilton syringe (30-gauge needle) to place multiple injection tracks into the CB hemisphere (Crus IIp in animals

AB1 and AB2, HVIIB in AB3). We injected small amounts (0.2 μL) of a mixture of RV ($4.5 \times 10^9$pfu/mL; provided byM. Schnell) and CTb (0.02%; List Biological Laboratories) at every 0.5 mm along the depth of each injection track (Table 3-1). The depths of these injections were based on prior structural magnetic resonance images of each CB. When all injections were completed, the CB was covered with artificial dura and the incision was closed in anatomical layers. The monkeys were placed in an isolation chamber and administered an analgesic (buprenorphine; 0.01 mg/kg) and dexamethasone (0.25 mg/kg) every 12 h.

Prior studies have demonstrated that RV is transported exclusively in the retrograde direction in a time-dependent fashion (Hoshi et al., 2005; Kelly and Strick, 2000; Prevosto et al., 2010). The available evidence suggests that the spread of RV is exclusively transsynaptic and that the virus is neither taken up by fibers of passage nor transported between neurons and glia (Kelly and Strick, 2000). The time to infect first-, second- and third-order neurons depends on the strain of RV and its concentration. The N2c strain used in the present experiments is transported at a higher transfer rate than other strains used for tracing (e.g., CVS-11). In the current experiments, we set the survival time following the CB injections to 42 h (Figure 3-1 and Table 3-1). This survival time was based on a series of experiments that examined a range of survival times following central injections of the N2c strain (Hoshi et al., 2005). A 42-h time period is long enough to allow transport of the virus only to second-order neurons.

### 3.2.4 Histological procedures

At the end of the survival time, the monkeys were deeply anesthetized using ketamine (25 mg/kg, i.p.) followed by pentobarbital sodium (40 mg/kg, i.p.). They were perfused transcardially with 0.1M phosphate buffer (pH 7.4), followed by 10% buffered formalin, and

finally a mixture of 10% buffered formalin and 10% glycerol at 4 °C. The brain and spinal cord were removed from the skull and stored overnight in 10% buffered formalin and 10% glycerol at 4 °C and then placed in 10% buffered formalin and 20% glycerol at 4 °C for 2 weeks. Blocks of tissue (cerebral cortex, brainstem, and CB) were individually frozen and sectioned at 50 μm. Every 10th section was stained with cresyl violet for cytoarchitecture analysis. Brain sections were immunohistochemically reacted according to the avidin-biotin peroxidase method (Vectastain; Vector Laboratories). Alternating sections were reacted with mouse anti-M957 (supplied by A. Wandeler, 1:300) and goat anti-choleragenoid (List Biological Laboratories, 1:10,000) to detect rabies virus or CTb, respectively. Reacted tissue sections were mounted on gelatin coated glass slides, air dried, and cover-slipped.

### 3.2.5 Data analysis

Brain sections through the cerebral cortex, brainstem, and the CB were examined for immunostaining using bright field and polarized illumination. Images of selected anatomical structures were obtained using a digital camera (RT3 monochrome camera, Diagnostic Instruments) coupled to a personal computer. The images were adjusted for contrast, brightness, and intensity using Corel Photopaint. Data were plotted using a computerized plotting system (MD2; Accustage). This system uses optical encoders to measure the X–Y movements of the microscope stage and stores the coordinates of section outlines and labeled neurons.

### 3.2.6 Injection sites

We used the CTb labeling to identify and reconstruct the injection sites (Prevosto et al., 2010). The plotted sections with outlines of the injection site were used to create a flattened map of the CB (following a procedure adapted from Kelly and Strick, 2003). Flattened maps of the CB cortex and corresponding injection sites were created for each animal, using custom laboratory software. The injection sites were then outlined on a representative map of a cebus monkey CB cortex (adapted from Kelly and Strick, 2003).

## 3.3 RESULTS

We injected the N2c strain of RV into selected sites within the CB cortex of three cebus monkeys (Figure 3-2A and Table 3-1). RV is transported transneuronally in the retrograde direction in a time-dependent fashion in nonhuman primates (Hoshi et al., 2005; Kelly and Strick, 2000; Kelly and Strick, 2003; 2004; Prevosto et al., 2010).

**Table 3-1: Experimental animals and virus transport.**

| Exp | Age (yrs) | Sex | Weight (kg) | Injection Site | Number of Injections | Volume Injected (µL) | Survival Time (h) | Virus Concentration (PFU) |
|---|---|---|---|---|---|---|---|---|
| **AB1** | 14 | F | 2.6 | Crus IIp | 59 | 11.8 | 42 | $4.5 \times 10^9$ |
| **AB2** | 6 | M | 3.4 | Crus IIp | 60 | 12 | 42 | $4.5 \times 10^9$ |
| **AB3** | 2.5 | M | 1.9 | HVIIB | 46 | 9.2 | 42 | $4.5 \times 10^9$ |

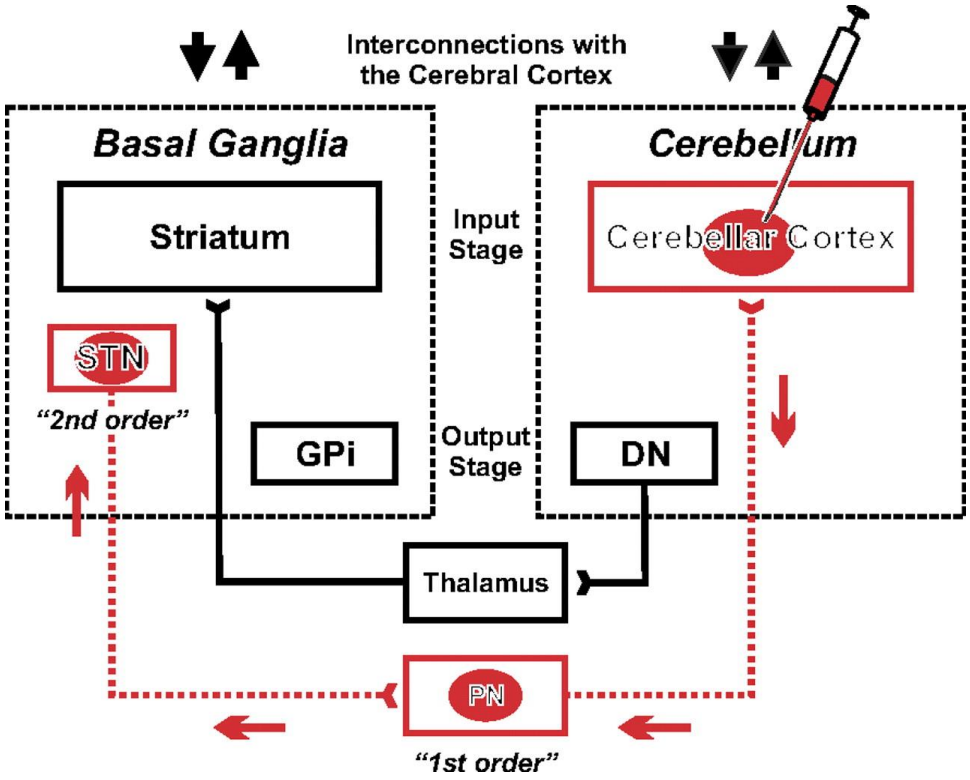


**Figure 3-1: Experimental paradigm and circuits interconnecting basal ganglia and cerebellum.**
We injected rabies virus (RV) into regions of the cerebellar hemisphere. The virus went through two stages of transport: retrograde transport to first-order neurons that innervate the injection site and then, retrograde transneuronal transport to second-order neurons that innervate the first-order neurons. The red arrows indicate the direction of virus transport. Previously, we have shown that an output stage of cerebellar processing, the dentate nucleus (DN), has a disynaptic connection with an input stage of basal ganglia processing, the striatum (Hoshi et al., 2005). In this experiment, we demonstrate a reciprocal connection from the subthalamic nucleus (STN) to the input stage of cerebellar processing, the cerebellar cortex. These interconnections enable two-way communication between the basal ganglia and cerebellum. Each of these subcortical modules has separate parallel interconnections with the cerebral cortex (up and down black arrows). DN, dentate nucleus; GPi, internal segment of the globus pallidus; PN, pontine nuclei; STN, subthalamic nucleus. From Bostan et al., 2010.

We set the survival time at 42 h to allow two stages of transport: retrograde transport of RV to first-order neurons that project to the injection site and then, retrograde transneuronal transport of the virus to second-order neurons that make synaptic connections with the first-order neurons. The suitability of the survival time was confirmed by the presence of second-order neurons labeled in cortical layer V, the site of corticopontine neurons (Glickstein et al., 1985), and by the absence of third-order neurons labeled in layer III.

### 3.3.1 Second-order neurons labeled in the subthalamic nucleus following rabies virus injections into the cerebellar cortex

Our injections targeted Crus IIp (n = 2) and the hemispheric expansion of lobule VIIB (HVIIB) (n = 1) (Figure 3-2A). In all cases we mixed RV with a conventional tracer, the β subunit of cholera toxin (CTb, 0.02%). We used this mixture to facilitate identification of the RV injection site and to label neurons that project directly to it (first-order neurons). After RV-CTb injections into Crus IIp and HVIIB, we found first-order neurons labeled with CTb and RV in regions of the pontine nuclei and the inferior olive that are known to project to the injected regions of the CB cortex (Brodal, 1979; 1980; Brodal and Brodal, 1981).

We found second-order neurons labeled with RV in cortical areas and in regions of the parvocellular portion of the red nucleus (Figure 3-3A) that are known to project to the first-order neurons in the pontine nuclei and the inferior olive (Glickstein et al., 1985; Strominger et al., 1979). Surprisingly, we also found substantial numbers of second-order neurons labeled with RV in the STN predominantly on the side contralateral to the injection site (Figures 3-2B, 3-3, and 3-5). We counted labeled neurons on every other section through the STN of the two animals illustrated in the figures and found 1,160 second-order neurons in the STN after the Crus IIp injection (AB2) and 923 second-order neurons after the HVIIB injection (AB3).

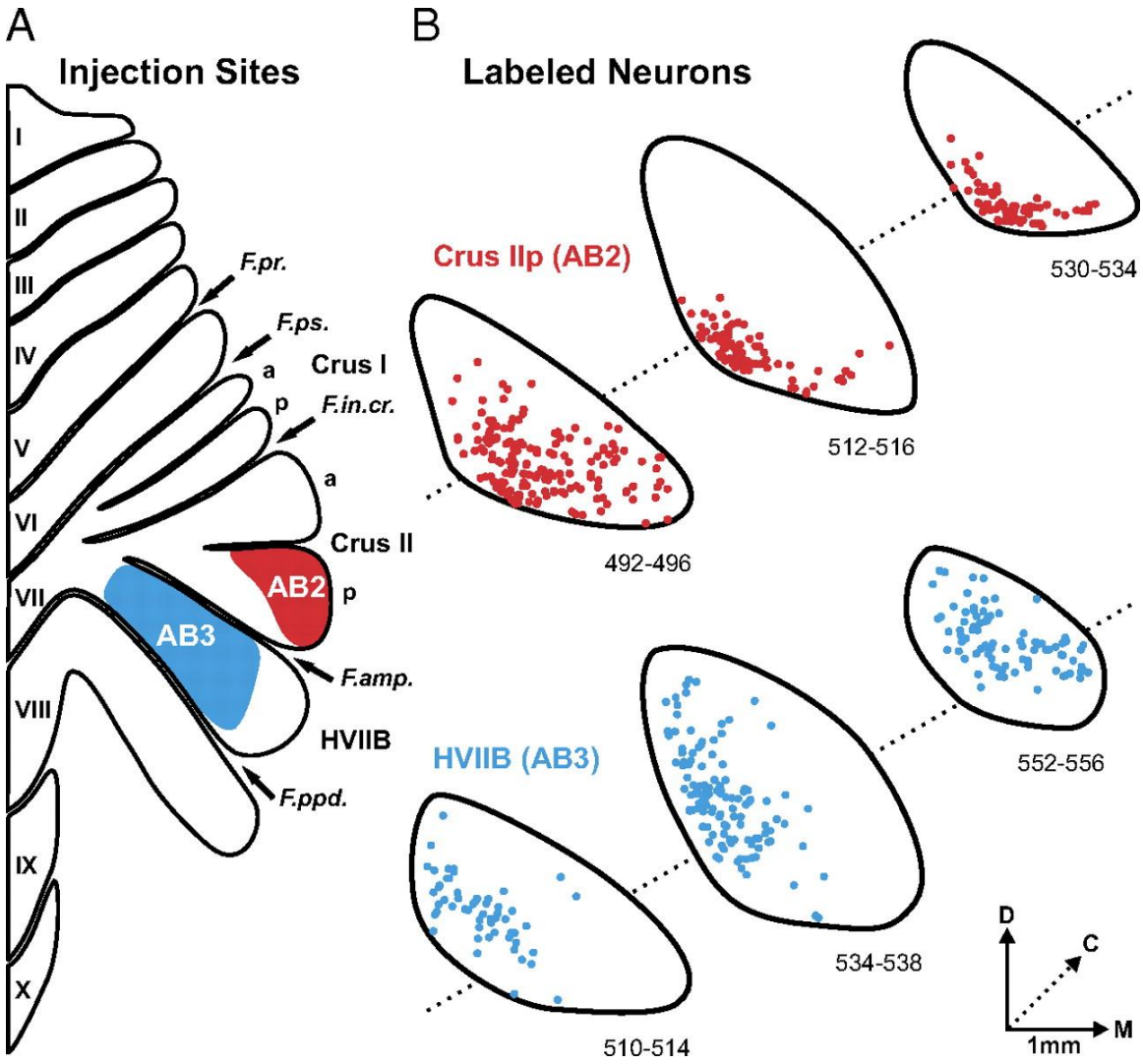


**Figure 3-2: Injection sites and second-order neurons labeled in the STN.**
(A) The injection sites of rabies virus (RV) with cholera toxin subunit β (CTb) are outlined on a flattened map of the cerebellar cortex adapted from Kelly and Strick, 2003. The injection in AB2 (red filled area) targeted Crus IIp. The injection site in another animal (AB1, not illustrated) also targeted Crus IIp. In this case the injection site overlapped, but was somewhat less extensive than that of AB2. The injection in AB3 (blue filled area) targeted HVIIB. (B) Cross-sections of the STN show the location of second-order neurons labeled by the retrograde transneuronal transport of RV from Crus IIp in AB2 (red dots) and from HVIIB in AB3 (blue dots). Each of the three rostrocaudal levels displayed is spaced ≈1 mm apart. Labeled neurons from three consecutive sections (spaced 100 μm apart) are overlapped at each level. a, anterior; C, caudal; D, dorsal; F.amp., ansoparamedian fissure; F.in.cr., intracrural fissure; F.ppd., prepyramidal fissure; F.pr., primary fissure; F.ps., posterior superior fissure; M, medial; p, posterior. From Bostan et al., 2012.

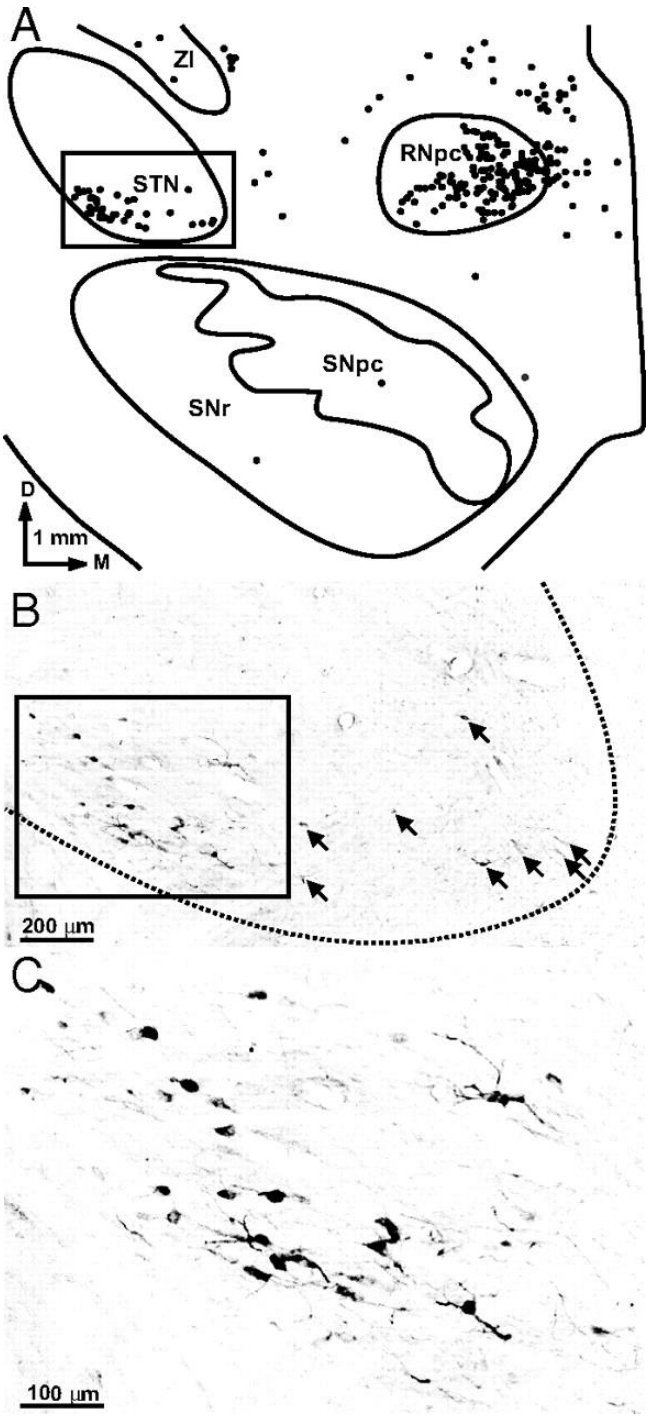


**Figure 3-3: Second-order neurons in the STN labeled by the retrograde transneuronal transport of RV**

(A) Chart of a coronal section through the midbrain in one monkey (AB2). Each dot represents a neuron infected with RV. (B) Photomicrograph of the boxed area in A. Arrows point to examples of second-order neurons labeled with RV. (C) Enlargement of the boxed area in B. D, dorsal; M, medial; RNpc, parvocellular red nucleus; SNpc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; ZI, zona incerta. From Bostan et al., 2012.

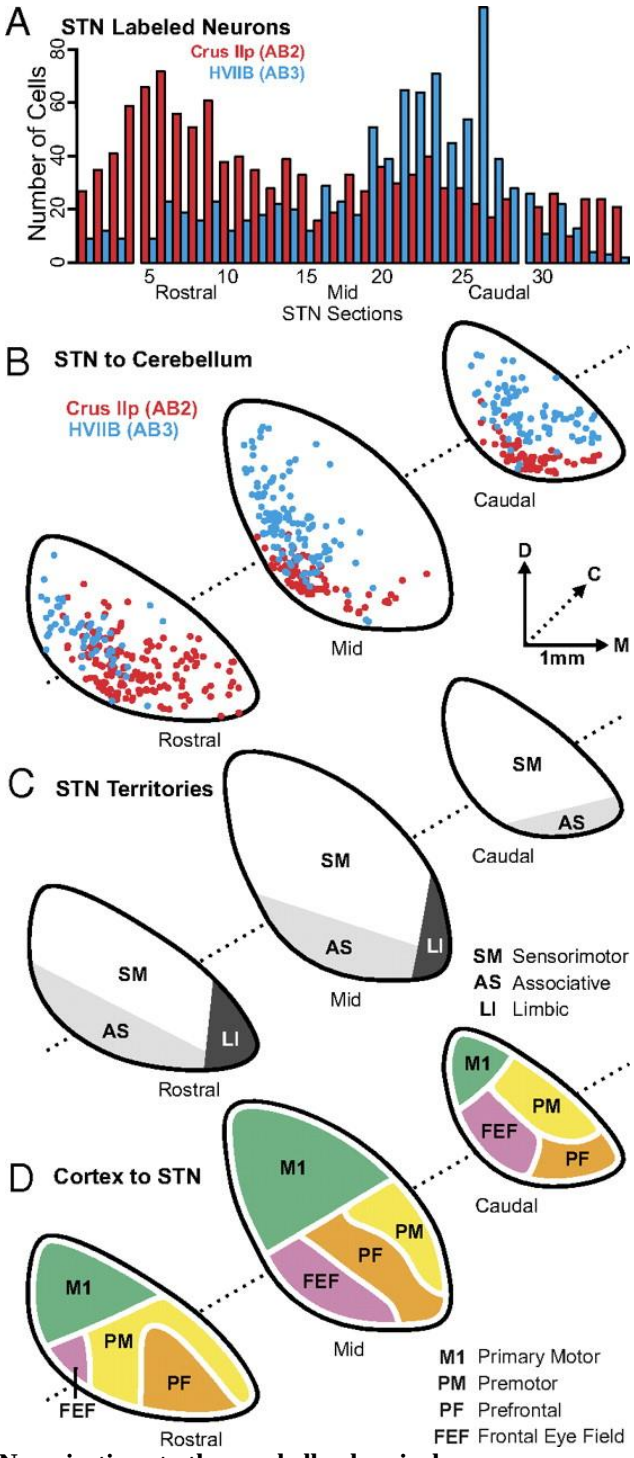


**Figure 3-4: Topography of STN projections to the cerebellar hemisphere.**

(A) Histogram of the rostrocaudal distribution of second-order neurons in STN in AB2 (red bars) and AB3 (blue bars). The distance between two consecutive sections represented is 100 μm. Missing bars correspond to missing sections. (B) Charts of labeled neurons in AB2 (red dots) and AB3 (blue dots) are overlapped to illustrate the topographic differences in distribution of second-order neurons in STN of the two cases. (C) Schematic representation of STN organization, according to the tripartite functional subdivision of the basal ganglia (adapted from Parent and Hazrati, 1995a). (D) Schematic summary of the known connections of the STN with areas of the cerebral cortex. C, caudal; D, dorsal; M, medial. From Bostan et al., 2012.

### 3.3.2 Topographical organization of the projection from the subthalamic nucleus to the cerebellar cortex

The STN has been subdivided into three functional territories: sensorimotor, associative, and limbic (Figure 4C). These subdivisions are based on STN interconnections with regions of the globus pallidus and the ventral pallidum (Hamani et al., 2004; Joel and Weiner, 1997; Parent and Hazrati, 1995a). The pattern of inputs from the cerebral cortex to the STN also imposes a functional topography on the STN (Figure 4D) (Inase et al., 1999; Monakow et al., 1978; Nambu et al., 1996; Nambu et al., 1997; Stanton et al., 1988). A comparison of our data with these functional subdivisions indicates that most of the STN neurons that project to Crus IIp are located in its associative territory, which receives input from the frontal eye fields and regions of prefrontal cortex. In contrast, most of the STN neurons that project to HVIIB are located in its sensorimotor territory, which receives input from the primary motor cortex and several of the premotor areas in the frontal lobe. Although we have examined only a relatively small portion of the CB cortex, these results suggest that the STN-CB connection is involved in integrating BG and CB functions in both motor and nonmotor domains.

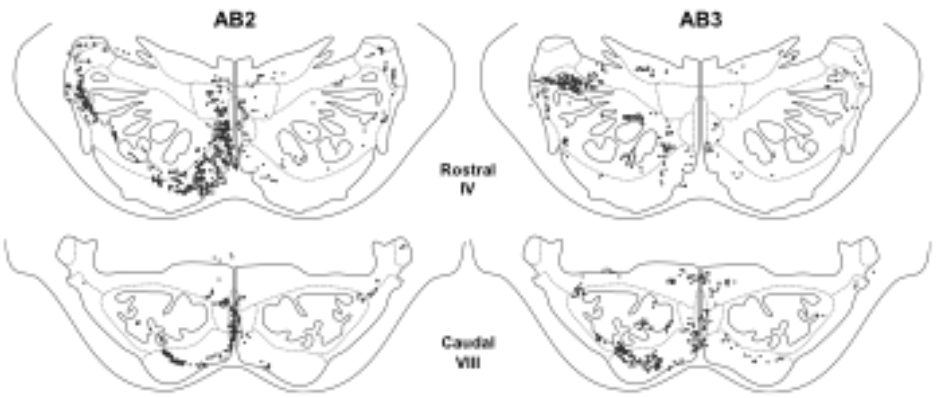


**Figure 3-5: Pontine nuclei projections to regions of cerebellar cortex.**

Charts display the locations of first-order neurons (small dots) in the pontine nuclei labeled after retrograde transport of cholera toxin subunit ß (CTb) from injections into the cerebellar cortex. The results from injections into Crus IIp (AB2) are on the left, and those from injections into HVIIB (AB3) are on the right. To generate these charts we resized and overlapped data from each animal onto outlines of the pontine nuclei (Schmahmann and Pandya, 1991). Roman numerals (IV and VIII) represent the rostro-caudal levels according to Schmahmann and Pandya, 1991.

The nuclei that mediate the disynaptic connection between the STN and the CB remain to be determined. However, the STN is known to project to the nucleus reticularis tegmenti pontis (NRTP) and several basal pontine nuclei (Giolli et al., 2001). As noted above, we observed first-order neurons labeled with CTb and RV in the NRTP and multiple basal pontine nuclei after our tracer injections (Figure 3-5). Thus, we view the pontine nuclei as the most likely candidates for mediating the disynaptic connection, but this proposal remains to be tested in future experiments.

## 3.4 DISCUSSION

The STN has been described as the "driving force of the basal ganglia" (Kita and Kitai, 1987). Our results indicate that this driving force extends well beyond the nuclei of the BG to the CB. As a consequence, the anatomical substrate exists for both normal and abnormal signals from the STN to influence CB processing. The topographic organization of this disynaptic pathway suggests that STN output could have an impact on CB function during motor and nonmotor

behavior. In the following paragraphs we will briefly describe some of the potential implications of this pathway for CB involvement in (i) prototypical BG disorders and (ii) reward processing.

Parkinson's disease (PD) and dystonia are traditionally considered to be "basal ganglia disorders." PD is associated with degeneration of a specific set of dopaminergic neurons in the pars compacta of the substantia nigra. Acquired (secondary) dystonia also is often associated with lesions of the BG (Bhatia and Marsden, 1994). Although no overt neurodegeneration has been identified in idiopathic (primary) dystonia, there is evidence for alterations in the BG in this form of the disorder as well (Breakefield et al., 2008). Despite these results, a number of observations have suggested that alterations in CB activity may contribute to the motor symptoms of both PD and dystonia. For example, imaging studies report marked abnormal increases in CB activity in PD patients and in subjects with idiopathic dystonia (Eidelberg, 1998; Payoux et al., 2004). In PD, deep brain stimulation of the STN improves the motor signs and normalizes CB activation (Grafton et al., 2006; Payoux et al., 2004). In addition, one of the cardinal symptoms of PD, tremor at rest, is abolished by stimulating or lesioning the ventral intermediate nucleus of the thalamus, which is a target of CB efferents (Benabid et al., 1991). Similarly, in a mouse model of dystonia, pharmacological stimulation of the CB vermis elicited dystonic postures of the trunk and limbs (Pizoli et al., 2002).

The discovery of a disynaptic connection between the BG and CB provides a unique framework for interpreting these results. It is notable that in both PD and idiopathic dystonia, neural activity in the STN is higher than normal and is characterized by abnormal bursting and oscillatory activity (Schrock et al., 2009). Abnormal signals from the STN to the CB cortex could evoke the increased CB activation that is present in both disorders and alter CB-thalamo-cortical projections. Further attempts to ameliorate the symptoms of PD and dystonia might

benefit by focusing specifically on normalizing activity in the disynaptic pathway from STN to the CB. In fact, part of the effectiveness of deep brain stimulation of the STN might be achieved through this mechanism.

Our findings also provide a potential explanation for the presence of CB activation in imaging studies that were explicitly designed to study the normal functions of the BG. For example, several imaging studies have examined whether regions of the BG and related cortical areas display functional activation consistent with their involvement in "temporal difference" models of reward-related learning (O'Doherty et al., 2003; Seymour et al., 2004). It is noteworthy that robust CB activation was present in these experiments along with activation in the dorsal and ventral striatum. The disynaptic connection between the STN and the CB provides an anatomical substrate for reward-related signals in the BG to influence CB function during learning. From a computational perspective, the BG and CB have been viewed as segregated modules that implement different learning algorithms—reinforcement learning in the case of the BG and supervised learning in the case of the CB (Doya, 2000; Houk et al., 2007).

To summarize, a previous study from our lab demonstrated that an output stage of CB processing, the dentate nucleus, has a disynaptic connection with the input stage of BG processing, the striatum (Hoshi et al., 2005). The current report provides evidence for the reciprocal connection. Taken together these results provide the neural basis for substantial two-way communication between the BG and CB. Thus, the two subcortical structures may be linked together to form an integrated functional network. One might then ask what new computational operations emerge by interconnecting a reinforcement learning module with a supervised learning module.

# 4.0 SUMMARY AND CONCLUSIONS

## 4.1 OPEN- AND CLOSED-LOOP COMPONENTS OF BASAL GANGLIA CIRCUITS WITH THE PREFRONTAL CORTEX

### 4.1.1 Summary of findings

Views of the basal ganglia (BG) have been shaped by knowledge of their interconnections with the cerebral cortex. As described in Chapter 1, the BG receive considerable inputs from widespread areas of the cerebral cortex and send projections back to the cerebral cortex, via the thalamus. This pattern of connections establishes closed and largely segregated cortico-BG-thalamo-cortical loops that provide the neural substrate for important BG contributions to motor, associative, and limbic functions (Alexander et al., 1986; Middleton and Strick, 2000b). Results presented in Chapter 2 of this dissertation, along with other recent anatomical experiments (Kelly and Strick, 2004; Miyachi et al., 2006; Saga et al., 2011), provide evidence for important BG outputs, outside of the closed-loop circuits with the cerebral cortex.

The experiments described in Chapter 2 used retrograde transneuronal transport of rabies virus (RV) to demonstrate that the ventral striatum (VStr) projects multisynaptically to regions of the dorsal prefrontal cortex (PFC) that do not project back to the VStr. This projection establishes an open-loop component of BG circuits with nonmotor regions of the dorsal PFC.

Furthermore, the projection from the VStr to the dorsal PFC reveals an anatomical substrate for limbic processing within the BG to influence cognitive functions in the cerebral cortex.

These findings complement previous studies that used retrograde transneuronal transport of RV to show that the VStr projects multisynaptically to the primary motor cortex (M1) and the dorsal premotor cortex (PMd), which do not project back to the VStr (Kelly and Strick, 2004; Miyachi et al., 2006; Saga et al., 2011). These projections establish an open-loop component of BG circuits with motor regions of the cerebral cortex. Furthermore, the projections from the VStr to motor regions of the cerebral cortex reveal an anatomical substrate for limbic processing within the BG to influence motor functions in the cerebral cortex.

Taken together, these results suggest that the current view of BG connections with the cerebral cortex needs to be updated to include both functionally segregated closed-loops and an open-loop component (Figure 3-11). The open-loop pathways from the VStr to motor and prefrontal regions of the cerebral cortex allow for limbic processing in the BG to influence both motor and cognitive functions in the cerebral cortex. This pathway provides the first anatomical evidence of interaction between the functionally segregated closed-loop cortico-BG-thalamo-cortical circuits in the primate. The next section will discuss this pathway in relation to alternative proposals for how the closed-loop cortico-BG-thalamo-cortical pathways may interact. The following section will discuss the proposed route for the VStr projection to motor and nonmotor areas of the cerebral cortex and some of its implications.

### 4.1.2 Interactions between the closed-loop circuits that link the basal ganglia with the cerebral cortex

The BG interact with the cerebral cortex through parallel and largely segregated loops, in which information is sent from different areas in the cerebral cortex through spatially distinct domains in the BG and then returned to the cortical area of origin, via the thalamus (Alexander and Crutcher, 1990; Alexander et al., 1986; Parent and Hazrati, 1995a). The perspective of parallel processing in cortico-BG pathways provides an anatomical basis for BG contributions to multiple aspects of behavior (Middleton and Strick, 2000b). It has been especially useful in understanding and guiding treatment for BG disorders, which are believed to arise from abnormalities in one or more closed-loop circuits (DeLong and Wichmann, 2009; 2010; DeLong and Wichmann, 2007; François et al., 2004; Grabli et al., 2004; Wichmann and DeLong, 2007; Worbe et al., 2009; Worbe et al., 2011; Worbe et al., 2012; 2013). However, the perspective of parallel closed-loops linking the BG with functionally diverse areas of the cerebral cortex does not provide a means for cross-functional interactions. Are the closed-loop cortico-BG pathways entirely segregated, or do they interact to some extent?

There have been several proposals for how information from separate cortico-BG loops can influence each other (Calzavara et al., 2007; Haber, 2003; Haber and Calzavara, 2009; Haber et al., 2000). A common theme in these proposals has been the apparent overlap between adjacent cortico-BG-thalamo-cortical circuits. For example, while projections from the cerebral cortex to the striatum and subsequent BG nuclei follow the topographical organization described in Chapter 1, dendritic arborization of neurons within each structure may extend to adjacent functional areas. There is no evidence that individual neurons in the striatum receive inputs from functionally distinct regions of the cerebral cortex. However, it is possible that BG neurons at

the edges of cortical terminal fields process functionally related signals from different neocortical areas. For example, as discussed in Chapter 1, anatomical and physiologic studies of the sensorimotor cortico-BG-thalamo-cortical circuits are somatotopically organized. Partial overlap and specific interactions between adjacent sensorimotor subcircuits has also been reported (Nambu, 2011; Romanelli et al., 2005). Particularly, there is an area of overlap between M1 and supplementary motor area (SMA) projections to the putamen (Takada et al., 1998). Additionally, some neurons in the putamen respond to stimulation in both M1 and SMA (Nambu et al., 2002). Although projections from functionally related motor areas partially converge, they preserve the somatotopic organization of the sensorimotor territory throughout the BG. These findings suggest that while regions on the edges of BG territories may process converging information from adjacent and related areas of the cerebral cortex, parallel processing remains an essential characteristic of BG circuits. Importantly, partial overlap between BG circuits originating in functionally related areas of the cerebral cortex does not appear to be sufficient for information transfer across functional domains.

Other proposals for integration of information within the BG involve non-reciprocal connections between cortico-BG-thalamo-cortical circuit components (Haber and Calzavara, 2009; Haber et al., 2000). There is no clear physiologic evidence to support these proposals. For example, it has been proposed that interactions between limbic, associative and motor circuits occur at the level of the substantia nigra pars compacta (SNpc). Studies in rats have shown that the NAcc can send projections to neurons in the substantia nigra (SN) that then target the dorsal striatum (Nauta et al., 1978; Somogyi et al., 1981). There is no evidence of similar synaptic arrangements in the primate. In fact, it is very unlikely that the VStr would target SN neurons that project back to the sensorimotor striatum in the monkey, given the topographical

organization of striato-nigro-striatal circuits (Haber et al., 2000). Instead, the hypothesis is that the SNpc may participate in "spiral" interactions with the striatum, so that SNpc afferents from limbic areas of the striatum are projected back to striatal associative regions, and SNpc afferents from striatal associative regions are projected back to striatal motor regions (Figure 4-1).

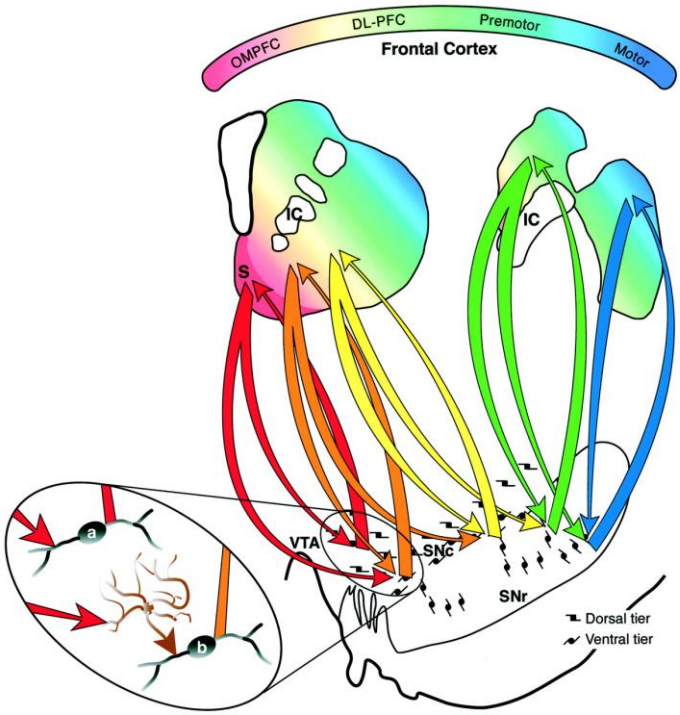


**Figure 4-1: Diagram of the "spiral" striato-nigro-striatal hypothesis.**
The colored gradient in rostral and caudal outlines of the striatum illustrates the organization of functional cortico-striatal inputs (red – limbic, green – associative, blue – motor). The magnified oval region shows hypothetical synaptic interactions of striato-nigral-striatal projections in reciprocal (a) vs. feed-forward (b) loops. In the reciprocal connection (red arrow) striatal neurons project directly onto a dopaimne cell (a), resulting in inhibition. The non-reciprocal projection (orange arrow) terminates indirectly on a dopamine cell (b) via a GABAergic interneuron (brown cell), resulting in disinhibition. DL-PFC, doroslateral prefrontal cortex; IC, internal capsule; OMPFC, orbital and medial prefrontal cortex; S, shell, SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; VTA, ventral tegmental area. From Haber et al., 2000, with permission.

According to this hypothesis, the limbic VStr could influence the associative and sensorimotor striatum via an iterative process involving the midbrain dopamine system. Hypothetically, projections from one striatal region could facilitate information transfer in an adjacent (and functionally distinct) striatal region by disinhibiting its dopaminergic projection (Figure 4-1, magnified region). As stated previously, there is no physiologic evidence to back up

this proposal. Furthermore, if an ascending spiral of connections exists as hypothesized by Haber and colleagues (2000), limbic processing in the VStr (e.g., in the NAcc shell) may influence processing in the associative territory of the striatum through a minimum of 6-8 synapses, and in the motor territory through a minimum of 8-10 synapses (see Figure 4-1). The degree of influence that VStr limbic processing would have over the associative and motor striatum through a long chain of connections involving dopaminergic transmission is unclear.

One appealing aspect of the spiral hypothesis is the fact that it points to the VStr as an interface between emotion and cognitive or motor function. The VStr is an ideal candidate for the mediation of emotion effects on cognition and action because of its involvement in reward, reinforcement, and the development of addictive behaviors (Koob and Volkow, 2010; Schultz et al., 1997). The results presented in Chapter 2 of this dissertation, along with previous findings (Kelly and Strick, 2004; Miyachi et al., 2006; Saga et al., 2011), described the evidence for an anatomical pathway in the primate that may allow the VStr to influence cognitive regions in the dorsal PFC, motor regions of the frontal cortex, and potentially numerous other areas in the cerebral cortex. Importantly, neurons in the VStr reach the dorsal PFC and motor cortical areas trisynaptically; this is the same number of synapses involved in the closed-loop (*direct* pathway) projection from the caudate and putamen to the dorsal PFC and motor cortical areas, respectively. Furthermore, almost half of the striatal inputs to M1 and areas in the dorsal PFC originate from the VStr. This indicates that the open-loop projection from the VStr to the cerebral cortex is likely to have important functional consequences. Some insights into the function of this projection come from considering the most likely route for the VStr to reach the frontal cortex, outside of the cortico-BG-thalamo-cortical loop.

### 4.1.3 The open-loop projection from the ventral striatum to the cerebral cortex

How does the VStr gain access to the dorsal PFC and motor areas of the cerebral cortex? In accordance with the parallel processing model of cortico-BG loops (Alexander et al., 1986), the VStr receives inputs from limbic areas of the cerebral cortex and sends projections back to the same areas thorough limbic portions of BG nuclei that do not project to motor cortical areas or to the dorsal PFC. The projection from the VStr to regions outside of the limbic cortico-BG loop likely bypasses the cortico-BG-thalamo-cortical loops altogether. Unlike motor and associative regions of the striatum, the VStr has been shown to send projections to regions outside of the BG. These projections include the nucleus basalis of Meynert (NBM), the hypothalamus, and mediodorsal thalamus (Haber et al., 1990). The NBM is the most likely candidate link between the VStr and cerebral cortical areas outside of the limbic loop.

The NBM contains the Ch4 neuron complex that provides the major source of cholinergic afferents to the cerebral cortex and the amygdala (Johnston et al., 1979; Mesulam et al., 1983; Mesulam and Van Hoesen, 1976; Pearson et al., 1983). Cholinergic and gamma-aminobutyric acid (GABA) neurons in the NBM send direct projections to the cerebral cortex. Based on our results, it is unlikely that VStr neurons synapse onto NBM neurons that project directly to the motor cortical areas or the dorsal PFC. Two different scenarios would fit with our results. VStr projections to the NBM may target the neurons that project to M1 and the dorsal PFC only indirectly, via NBM interneurons. Alternatively, VStr projections may target only a subset of NBM neurons that project to M1 and the dorsal PFC disynaptically. Based on the available anatomical data, it is unclear which of these scenarios is more likely.

Cholinergic neurons in the basal forebrain are innervated by GABAergic projections that could originate in the VStr (Smiley and Mesulam, 1999). There is no additional data regarding

the targets of the VStr in the NMB of the primate. Studies in rats indicate that the VStr may reach cholinergic neurons, interneurons and GABAergic cortical projection neurons in the NBM (Henny and Jones, 2008; Ingham et al., 1988; Záborszky and Cullinan, 1992). There is light microscopic evidence of NAcc inputs to intrapallidal Ch4 neurons (Grove et al., 1986) and substance P-containing terminals (likely of striatal origin) have been shown to contact these neurons (Bolam et al., 1986a). Substance P-containing terminals were also observed on non-cholinergic neurons in the basal forebrain (Bolam et al., 1986a). These results indicate that the VStr projections may target specific cholinergic neurons (intrapallidal Ch4 neurons), as well as non-cholinergic neurons in the basal forebrain. Future studies are needed to characterize the VStr projections to the NBM in the primate, in order to clarify the pathway from the VStr to the dorsal PFC and motor regions in the cerebral cortex.

A series of behavioral and pharmacological studies in rats provide additional insights into the projection from the VStr to the NBM, its effects on the cerebral cortex and potential functional implications. VStr efferents are GABAergic and modulation of GABAergic activity in the basal forebrain (NBM) has been shown to have important effects on attention by mediating cholinergic activity in the cerebral cortex, particularly in the PFC. Benzodiazepine agonist infusion into the basal forebrain decreases acetylcholine (ACh) efflux in the rat cerebral cortex and lowers behavioral vigilance, as measured by a visual signal discrimination task (Holley et al., 1995). Stimulation of ionotropic glutamate receptors in the NAcc has been shown to increase cholinergic transmission the rat PFC; these increases are positively modulated by dopamine D1 receptor activation and attenuated by D2 receptor activation in the NAcc (Alexander et al., 2009; Brooks et al., 2007; Zmarowski et al., 2007). Furthermore, NAcc stimulation enhances sustained attention in the presence of distractors, through its effects on the cholinergic projection to the

cerebral cortex (St Peters et al., 2011). Altogether, these studies indicate that VStr projections to the NBM may serve to increase ACh release in the cerebral cortex. A projection from the VStr to basal forebrain GABAergic interneurons fits with this pattern of results (and our results discussed in Chapter 2), as it would serve to disinhibit NBM cholinergic projection neurons and increase ACh efflux in the cerebral cortex.

Modulation of cerebral cortical areas by the VStr via the central cholinergic system is likely to have important functional consequences. Ch4 neurons provide a rich and dense innervation of all regions of the cerebral cortex (Mesulam, 2004; Mesulam and Geula, 1988; Mesulam et al., 1992; Mesulam and Van Hoesen, 1976; Rye et al., 1984). Therefore, the open-loop projection from the VStr may, in fact, reach the entire cerebral cortex.

Modulation of cortical activity via the cholinergic system is unlikely to encode specific information, but may influence selective attention, learning, memory, perception, and consciousness (Everitt and Robbins, 1997; Sarter et al., 2003; Woolf, 1996; Woolf and Butcher, 2011). Cholinergic projections act on these varied systems by enhancing signal-to-noise ratio and contributing to cortical synchrony and neuroplastic responses, such as dendritic growth, in the cerebral cortex (Grossberg and Versace, 2008; Patil et al., 1998; Sarter et al., 2005; Woolf, 1996; Woolf and Butcher, 2011). Activation of the cortical cholinergic input appears to require presentation of novel or salient stimuli (Arnold et al., 2002; Himmelheber et al., 1997). Neurons in the VStr respond to novel and salient stimuli (Williams et al., 1993) and may contribute to the recruitment of the central cholinergic system in the presence of these kinds of stimuli to enhance their processing and memorability.

Evidence suggests that the VStr open-loop projection to the PFC may be involved in attentional flexibility. In a human imaging study, activity in the VStr elicited by salient events

has been shown to modulate the connectivity between the PFC and visual association areas (van Schouwenburg et al., 2010). Modulation via the cholinergic system would allow VStr activity to influence the top-down modulation of visual association areas by the PFC. This mechanism may be altered when VStr activity is compromised, such as in addiction (Koob and Volkow, 2010). Support for this hypothesis comes from findings that psychostimulants (and increased NAcc dopamine) increases ACh release in the rat cerebral cortex (Nelson et al., 2000). Dopaminergic changes in the VStr that are associated with addiction may influence activity in motor and associative cortical regions via the central cholinergic system, and may have downstream effects on sensorimotor and associative cortico-BG circuits. In these ways, the open-loop pathway from the VStr may contribute to drug-seeking and repeated drug use.

The open-loop pathway from the VStr to the cerebral cortex is also likely to have important consequences in conditions where the central cholinergic system is compromised, including Alzheimer's disease (Mesulam, 2012; Mesulam, 2004), Parkinson's disease (PD) (Bohnen and Albin, 2011) and schizophrenia (Hyde and Crook, 2001; Raedler et al., 2000; Sarter et al., 2005). Potential implications are particularly intriguing in a disorder such as PD. PD is characterized by motor disturbances that are related to the degeneration of SNpc dopaminergic neurons primarily in the motor circuit (Wichmann et al., 2011). Motor disturbances are often accompanied by nonmotor features, such as cognitive deficits, depression, anxiety and psychosis (Wolters and Francot, 1998). Some of these nonmotor features are likely due to dopaminergic degeneration within the nonmotor BG circuits, but also to additional non-dopaminergic deficits. In particular, cholinergic denervation in PD has been shown to occur at the same stage as nigral degeneration (Braak et al., 2003) and significant loss of NBM cholinergic neurons has been reported in PD brains (Candy et al., 1983; Nakano and Hirano, 1984; Rogers et al., 1985;

Tagliavini et al., 1984; Whitehouse et al., 1983). The impairment in the basal forebrain cholinergic system may play a significant role in PD cognitive decline and development of dementia (Korczyn, 2001; Mattila et al., 1998; Perry et al., 1977). For example, VStr modulation of cortical activity via the NBM may be involved in changes in top-down attentional control in PD. PD patients show deficits in top-down attentional control and their attention appears to be more easily captured by salient information (Cools et al., 2010). Future studies are needed to determine if these changes in PD are related to abnormal VStr activity (due to dopamainergic degeneration or medications), changes in the cholinergic system, or both.

To summarize, evidence indicate that the open-loop projection from the VStr to the cerebral cortex may recruit the central cholinergic system. Modulation of the VStr in rats results in changes in cholinergic activation of the cerebral cortex and associated effects on attention. Evidence in humans also suggests VStr activity may modulate attention. The open-loop pathway may provide a route for limbic processing in the BG to engage attention mechanisms and enhance processing of and responsiveness to behaviorally relevant stimuli. Future work is needed to substantiate this hypothesis and to evaluate the contributions of this pathway to disorders in which it may be compromised, such as addiction, Alzheimer's disease, PD, and schizophrenia. It will be important for future studies to consider that (dopaminergic) dysregulation of the VStr may cause dysfunction not only through its action within the limbic loop, but also through its effects on attention and executive function through the basal forebrain cholinergic system.

## 4.2 THE BASAL GANGLIA COMMUNICATE WITH THE CEREBELLUM

### 4.2.1 Summary of findings

The loops that link the BG with the cerebral cortex have traditionally been considered to be anatomically and functionally distinct from those that link the CB with the cerebral cortex (Doya, 2000; Graybiel, 2005). The outputs from the BG and CB to the cerebral cortex are relayed through distinct thalamic nuclei (Percheron et al., 1996; Sakai et al., 1996). Any interactions between cortico-BG and cortico-CB loops were thought to occur primarily at the neocortical level. Results presented in Chapter 3 of this dissertation, along with other recent anatomical experiments (Hoshi et al., 2005), challenge this perspective and provide evidence for disynaptic pathways that directly link the BG with the CB.

The experiments described in Chapter 3 used retrograde transneuronal transport of RV to demonstrate that the STN projects disynaptically to CB cortex. Projections to the CB cortex originate from motor and nonmotor domains within the STN. Furthermore, the projections terminate in motor and nonmotor regions of the CB cortex. These findings indicate that the disynaptic pathway from the STN to the CB cortex enables an output from the BG to influence nonmotor, as well as motor function within the CB.

These findings complement a previous study that used retrograde transneuronal transport of RV to show that the dentate nucleus projects disynaptically to the striatum (caudate and putamen) (Hoshi et al., 2005). Projections to the striatum originate from motor and nonmotor domains in the dentate. Furthermore, the projections terminate in regions of putamen and caudate known to be within the sensorimotor and associative territories. These findings indicate

that the disynaptic pathway from the dentate to the striatum enables an output from the CB to influence nonmotor, as well as motor, function within the BG.

Taken together, these studies indicate that the BG and the CB are components of a densely interconnected network, concerned with motor and nonmotor aspects of behavior. As a consequence, these major subcortical systems are likely to interact as part of their normal function. Such interactions imply that abnormal activity in one system would have important effects on the other. Several observations support these predictions. The following sections provide the evidence that implicates both the BG and the CB in associative reward-related learning and in the manifestations of neuropsychiatric and motor disorders.

### 4.2.2 Basal ganglia and cerebellar contributions to learning

The BG and CB are typically viewed as segregated modules that participate in different aspects of learning. The BG is thought to be involved in reward prediction and reward-based learning, whereas the CB is thought to be involved in adaptive modification of behavior and error-based learning (Doya, 2000). Future research is needed to determine the computational benefits of interconnecting a reinforcement learning module with a supervised learning module in order to better understand how the BG and CB may interact.

So far, accounts of reward-related learning have strongly emphasized the role of the BG because of the hypothesis that dopamine neurons reflect reward-prediction error and facilitate reinforcement learning in striatal target neurons (Schultz et al., 1997). Indeed, lesions and inactivations of the VStr significantly impair previously acquired conditioned responses to food (Blaiss and Janak, 2009; Parkinson et al., 1999). Human fMRI studies have also shown that activity in the striatum is correlated with reward prediction error in Pavlovian reward association

tasks (O'Doherty et al., 2004; O'Doherty et al., 2003). Strikingly, reward prediction error in these imaging studies is also strongly correlated with cerebellar signals (Figure 4-2) (O'Doherty et al., 2003). In light of the findings that the BG is closely interconnected with the CB, such a result need not be surprising. There is substantial evidence for CB contributions to associative learning (Swain et al., 2011; Thompson et al., 2000). Early studies indicate that the CB is both necessary and sufficient for the establishment of classical conditioning with aversive stimuli (Brogden, 1942). The CB is activated in neuroimaging studies of aversive conditioning in humans, along with regions in the striatum (Figure 4-2) (Pohlack et al., 2012; Seymour et al., 2004). Co-activations of the BG and the CB (Figure 4-2) (O'Doherty et al., 2003; Pohlack et al., 2012; Seymour et al., 2004; Tanaka et al., 2004) suggest that they may interact in support of processes involving reward-related learning. Although there is convincing evidence that both the BG and the CB contribute to reward-related learning (as reviewed by (Liljeholm and O'Doherty, 2012; Swain et al., 2011), further work is needed to determine precisely how these systems interact during this and other processes.

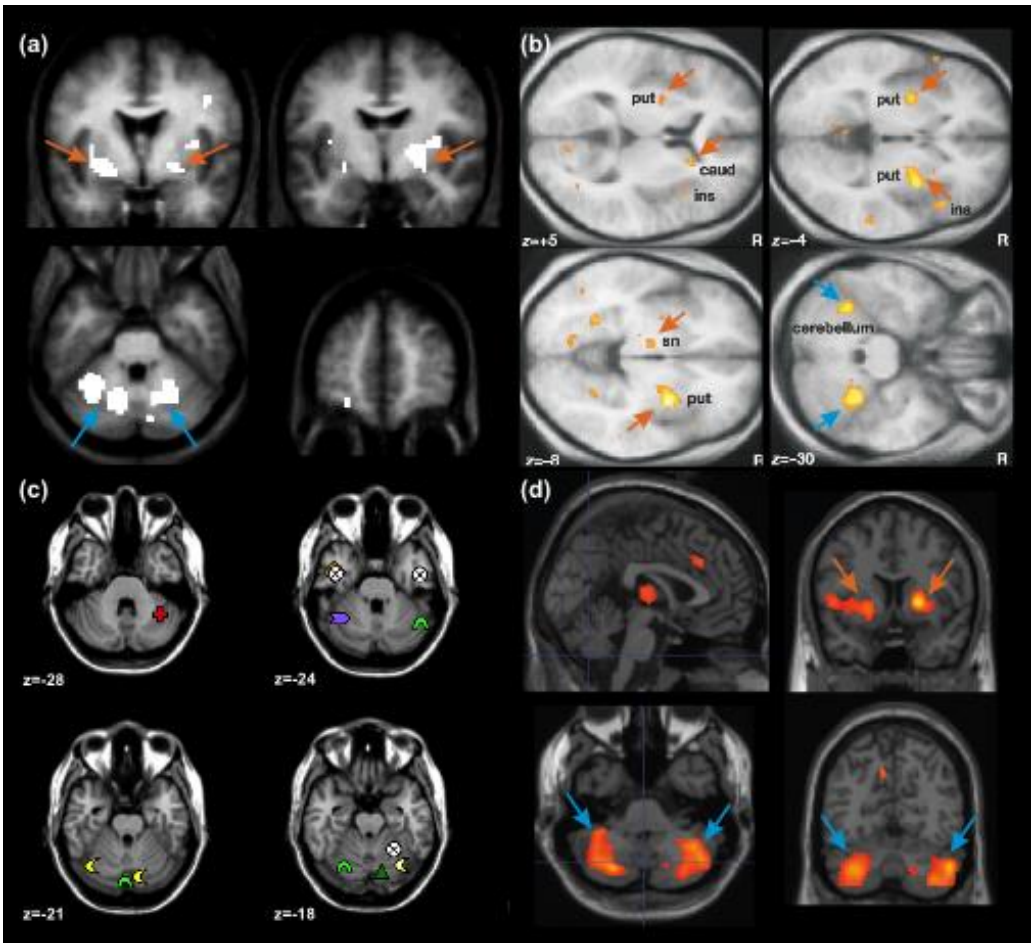


**Figure 4-2: Cerebellar activations associated with learning paradigms and neuropsychiatric conditions.**
(A) Functional MRI study of appetitive conditioning with a pleasant taste reward. Activation (white) in basal ganglia and cerebellum correlates with temporal differences prediction error. (B) Functional MRI studi of higher-order aversive conditioning. Activation (yellow/orange colors) in the basal ganglia and cerebellum correlates with temporal difference prediction error. (C) Cerebellar involvement in addiction. Summary results of cerebellar activation associated with cue-induced craving. Different shapes indicated results from different studies. (D) Tics in Tourette syndrome (tics minus sleep contrast) activate both the cerebellum and the basal ganglia. In all panels, blue arrows point to sites of cerebellar activation and orange arrows point to sites of basal ganglia activation. From Bostan et al., 2013.

BG and CB interactions in reward-related learning may explain, in part, why lesions in both regions impair reward-based reversal learning (Bellebaum et al., 2008; Thoma et al., 2008) and may help interpret findings that implicate the cerebellum in addiction. Although dopaminergic function and reinforcement learning implemented in the BG are considered key elements in the process of addiction (for reviews, see (Koob and Volkow, 2010; Maia and Frank, 2011)), the CB may also play an important role in this disorder (for a review, see (Miquel et al.,

2009)). Neuroimaging studies in addicted individuals provide compelling evidence for this perspective (see Figure 4-2C). For example, neuroimaging studies reported that cognitive deficits in addicted individuals were associated with abnormal CB activity (Hester and Garavan, 2004). Furthermore, imaging studies consistently reveal that the CB is active when addicts interact with conditioned drug cues that increase craving (Figure 4-2C). Such activations have been observed across addiction studies irrespective of the drug of abuse and include responses to smoking cues (David et al., 2005), alcohol cues (Schneider et al., 2001), heroin cues (Yang et al., 2009) and cocaine cues (Bonson et al., 2002; Grant et al., 1996). There have been two main explanations for CB activations in cue-reactivity paradigms. First, it has been proposed that the CB (through its connections with the prefrontal cortex) is active as part of a distributed memory network, subserving emotional and cognitive links between the environment and drug craving (Grant et al., 1996). Second, it has been proposed that the CB (through its connections with motor and premotor neocortical areas) is active as part of a distributed sensorimotor network, subserving automatized behavioral reactions towards drug-related stimuli (Yalachkov et al., 2009; 2010). Co-activations between the BG and the CB in cue-induced craving studies have been observed in several studies (David et al., 2005; Mcclernon et al., 2009; Olbrich et al., 2006; Yalachkov et al., 2009). Therefore, future accounts may benefit from considering interactions with the BG as another potential neural substrate for CB involvement in cue-induced craving and addiction.

### 4.2.3 Implications for basal ganglia disorders

BG interactions with the CB have also been shown to contribute to the symptoms of certain motor disorders, particularly Parkinson's disease and dystonia (for reviews, see (Filip et al.,

2013; Sadnicka et al., 2012; Wu and Hallett, 2013)). Briefly, in PD, the loss of dopaminergic neurons of the SNpc results in the manifestation of tremor, rigidity, bradykinesia and akinesia (Wichmann et al., 2011). However, CB activity is also abnormal in PD (Catalan et al., 1999; Ghaemi et al., 2002; Rascol et al., 1997). In parkinsonian patients (Lenz et al., 1988; Ohye et al., 1974) and in monkey models of the disease (Guehl et al., 2003), oscillatory activity at tremor frequencies has been recorded in regions of the thalamus that receive CB, not BG, efferents. Furthermore, the CB receiving thalamus is one of the most effective surgical sites for treating parkinsonian tremor (Narabayashi et al., 1987). These results suggest that abnormal activity in CB circuits may account for parkinsonian tremor. Furthermore, deep brain stimulation of the STN is not only highly effective in reducing the motor symptoms in PD (Krack et al., 2002), but also normalizes CB activity and function (Geday et al., 2009; Grafton et al., 2006; Hilker et al., 2004; Payoux et al., 2004; Trost et al., 2006). The disynaptic connection from the STN to the CB may be the anatomical substrate that mediates this effect of STN stimulation. Overall, these lines of evidence suggest that interactions between the BG and CB contribute to the expression of the motor abnormalities observed in Parkinson's disease.

Dystonia is another motor disorder that is often attributed to the basal ganglia (Neychev et al., 2011). Dystonia is characterized by involuntary muscle contractions, twisting movements and abnormal postures (Bhatia and Marsden, 1994). However, dystonia can also arise from CB dysfunction and may be better described as a network disorder involving the BG and the CB (LeDoux, 2011; Neychev et al., 2011). Human carriers of genetic mutations associated with dystonia exhibit abnormalities in both the BG and the CB (Argyelan et al., 2009; Carbon et al., 2010a; Carbon et al., 2010b; Carbon and Eidelberg, 2009; Carbon et al., 2008; Eidelberg, 1998; Ghilardi et al., 2003; Trost et al., 2002). In normal mice with pharmacological excitation of the

CB or mutant tottering mice, abnormal CB activity drives dystonic movements (Campbell and Hess, 1998; Chen et al., 2009; Neychev et al., 2008; Pizoli et al., 2002). Additional subclinical lesions of the BG in these animals exaggerate the expression of dystonia, indicating that BG contributes to the manifestation of motor abnormalities even when the primary defect originates in the CB (Neychev et al., 2008; Neychev et al., 2011)(Neychev et al., 2008; Neychev et al., 2011). In fact, aberrant CB activity may even cause dystonic movements through its effects on the BG. This view is supported by a mouse model of rapid-onset Dystonia-Parkinsonism in which abnormal CB activity can influence the BG, via the disynaptic pathway through the thalamus (Calderon et al., 2011). Overall, these findings support important functional interactions between the BG and the CB in the manifestation of motor disorders typically associated with the BG.

Disturbances of BG circuits are associated with a wide range of conditions including not only the motor disorders discussed above, but also disorders with nonmotor components such as Tourette syndrome, attention-deficit/hyperactivity disorders and schizophrenia (for a review, see (Maia and Frank, 2011)). There is evidence that the CB is involved in these conditions as well (reviewed in (Ito, 2008a; b; 2011; O'Halloran et al., 2012; Strick et al., 2009)). For example, in Tourette syndrome, the BG and CB are likely to be concurrently involved in tic generation (Figure 4-2D) (O'Halloran et al., 2012). Tourette syndrome patients can also be differentiated from controls by an abnormal metabolic pattern that includes increased CB and decreased BG metabolism (Lerner et al., 2007). Thus, BG interactions with the CB are likely to be as important for neuropsychiatric disturbances, as they are in the motor disorders.

To summarize, multiple lines of evidence provide support for functionally relevant interactions of the BG-CB network. Evidence indicates that the BG and the CB operate

concurrently in the process of associative reward-based learning, that they interact in the manifestation of motor disorders (PD and dystonia) and that their interaction may contribute to neuropsychiatric disorders (addiction and Tourette syndrome). Further work is needed to explore how the communication between the BG and CB contributes to these and other normal and abnormal behaviors.

## 4.3 CONCLUSIONS AND FUTURE DIRECTIONS

In conclusion, we have used transneuronal transport of RV to identify two novel pathways that allow the BG to influence motor and cognitive functions outside of the traditional cortico-BG-thalamo-cortical loops. First, we have shown that the VStr sends projections to regions of the dorsal PFC, as well as to motor regions of the cerebral cortex that do not project back to the VStr. Second, we have shown that the STN sends projections to the cerebellar cortex. These pathways are particularly striking because the VStr and the STN are generally considered input nuclei in the BG hierarchy and thought to send projections primarily to other BG nuclei. They pave the way for dramatic changes in our view of BG connections, with important functional consequences.

The first change in our view of BG connections is the observation that it is not exclusively involved in closed-loop circuits with functionally distinct regions of the cerebral cortex. Open-loop projections from the VStr reach motor areas in the cerebral cortex and areas of the dorsal PFC. Future studies are needed to establish the function of the open-loop projections. We propose that they provide a pathway for limbic processing in the BG to modulate cortical activity in behaviorally relevant contexts. This proposal is based on the fact that the

open-loop VStr projections to the cerebral cortex are likely mediated via the central cholinergic system, which has been involved in mechanisms of selective attention, learning, and memory. This system is known to target the entire cortical mantle, raising the question of whether the VStr can reach all or most cortical areas through pathways similar to those discussed in this dissertation. The central cholinergic projection system shows some degree of specificity and topographical organization. Future studies will be needed to clarify whether a similar (not immediately obvious) organization is present in the open-loop projection from the VStr to different cortical areas. Another important question that arises from the identification of the limbic open-loop is if and how it interacts with the closed-loop limbic circuit through the BG. Is there a projection from the VStr to limbic areas of the cerebral cortex that bypasses the cortico-BG-thalamo-cortical loop? If such a projection exists, does it involve the same mechanism as the open-loop projection to motor and associative areas of the cortex? Furthermore, are there different neurons in the VStr that give rise to the open- and closed-loop projections? There are many unanswered questions regarding the open-loop pathways form the VStr to the cerebral cortex; however, it is likely that the study of these pathways will prove to have important implications to understanding normal behavior and conditions such as addiction, PD, and schizophrenia.

Another dramatic change in our view of BG connections is the observation that this major subcortical structure is densely interconnected with the CB. The interconnections between the BG and the CB link the motor and nonmotor domains of one subcortical system with the corresponding domain in the other system. Thus, the anatomical substrate exists for BG output to influence the input stage of the CB, and vice-versa. Future studies are needed to study these connections physiologically. However, these interconnections provide the neural basis for CB

involvement in what have typically been considered to be BG operations, such as reward-related learning, and in BG disorders, such as Parkinson's disease, dystonia, or Tourette syndrome. These new results challenge us to discover the entire range of behavior that is influenced by the BG-CB network and the neural computations that are subserved by these interconnections.

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