Curriculum Vitae

Gwendolyn Gabrielle Calhoon

Degree and Date to be Conferred: Ph.D., 2013

Education

Saint Mary's College of Maryland: B.A., 2006
Major: Psychology, Minor: Neuroscience, *summa cum laude*
University of Maryland, Baltimore: Ph.D., 2013
Program in Neuroscience

Honors and Awards

2002, Kent County High School Valedictorian
2002, Maryland Distinguished Scholar Award, Maryland Higher Education Commission, merit-based scholarship
2002, Paul Nitze Scholarship to St. Mary's College of Maryland
2004, Psi Chi Psychology Honor Society induction
2005, Omicron Delta Kappa Leadership Honor Society induction
2006, Phi Beta Kappa Academic Honor Society induction
2006, St. Mary's College of Maryland Psychology Major Award (awarded to one graduating psychology major annually)
2006, Myron G. Marlay Scholarship Award for St. Mary's Project Research
2006, Faculty for Undergraduate Neuroscience Student Travel Award (to attend the SfN annual meeting in 2006)
2011, Elaine Otani Award, Graduate Program in Life Science at UMB (awarded to one graduate student annually)

Administrative Service

Institutional Service

2008 – 2012, Student Host for Applicants to the Program in Neuroscience, UMB
2011 – 2012, Student Representative to the Program in Neuroscience Training Committee, UMB
2011 – 2012, Chair of the Program in Neuroscience Student Training Committee, UMB
2011 – 2012, Graduate Program in Life Science Student Representative for the School of Medicine Council

Local and National Service

2011, Co-Chair, Gordon Research Seminar on Catecholamines
2011, Organizer for Program in Neuroscience Brain Awareness Week Outreach
2013, Chair, Gordon Research Seminar on Catecholamines

Teaching Service

2009 – 2012, Tutor, Core Courses in the Graduate Program in Life Science, UMB, 1 student annually, 2 months/year
2011, Teaching Assistant, Structure and Development: Embryology for 1st Year Medical Students, Anatomy Lab, UMB

Grant Support

09/20/2010 – 09/19/2013 Gwendolyn G. Calhoon (PI, 100%)
"The Nucleus Accumbens as a Behavioral Switchboard"
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Publications

Peer-reviewed Journal Articles

1. Feleder, C., Tseng, K. Y., **Calhoon, G. G.**, & O'Donnell, P. (2010). Neonatal intrahippocampal immune challenge alters dopamine modulation of prefrontal cortical interneurons in adult rats. *Biological Psychiatry*, 67 (4): 386-92.

2. Stalnaker, T. A., **Calhoon, G. G.**, Ogawa, M., Roesch, M. R., & Schoenbaum, G. (2010). Neural correlates of stimulus-response and response-outcome associations in dorsolateral versus dorsomedial striatum. *Frontiers in Integrative Neuroscience*, 4: 12. doi: 10.3389/fnint.2010.00012.

3. Gruber, A. J., **Calhoon, G. G.**, Shusterman, I., Schoenbaum, G., Roesch, M. R., & O'Donnell, P. (2010). More is less: A disinhibited prefrontal cortex impairs cognitive flexibility. *The Journal of Neuroscience*, 30 (50): 17102-17110.

4. McDannald, M. A., Whitt, J. P., **Calhoon, G. G.**, Piantadosi, P. T., Karlsson, R. M., O'Donnell, P., & Schoenbaum, G. (2011). Impaired reality testing in an animal model of schizophrenia. *Biological Psychiatry*, 70 (12): 1122-1126.

5. Stalnaker, T. A., **Calhoon, G. G.**, Ogawa, M., Roesch, M. R., & Schoenbaum, G. (2012). Reward prediction error signaling in posterior dorsomedial striatum is action-specific. *The Journal of Neuroscience*, 32 (30): 10296-305.

Other Brief Communications

1. **Calhoon, G. G.** & O'Donnell, P. (2010). Many roads to motor deficits: loss of dopamine signaling in direct or indirect basal ganglia pathway leads to akinesia through distinct physiological mechanisms. *Frontiers in Neuroscience*, 4: 168. doi: 10.3389/fnins.2010.00168.

Major Invited Speeches

1. **Calhoon, G. G.** "Heterosynaptic Suppression in the Ventral Striatum." *Winter Conference on Brain Research*. Snowbird, UT. 25 Jan 2012.

2. **Calhoon, G. G.** "The Nucleus Accumbens as a Switchboard: Heterosynaptic Suppression in the Ventral Striatum." Saint Mary's College of Maryland. 16 Nov 2012.

Abstracts

1. Senneff, A. M., Hege, J. R., **Calhoon, G. G.,** Horvitz, G. P., & Hiris, E. (2006). Can deceptive intention be detected in throwing motion in point-light motion displays? Annual Meeting of the Eastern Psychological Association, Baltimore, Maryland, March 2006.

2. **Calhoon, G. G.,** Horvitz, G. P., Senneff, A. M., Hiris, E., Hege, J. R., & Mandell, M. B. (2006). Judging sex and gender from throwing motion in point-light displays. Annual Meeting of the Eastern Psychological Association, Baltimore, Maryland, March 2006.

3. **Calhoon, G. G.,** & Brady, A. M. (2006). The effects of cognitive intervention in adolescence on behavioral abnormalities in a rat model of schizophrenia. Symposium for Young Neuroscientists and Professors of the Southeast (SYNAPSE), Davidson, North Carolina, April 2006.

4. **Calhoon, G. G.,** & Brady, A. M. (2006). The effects of cognitive intervention in adolescence on behavioral abnormalities in a rat model of schizophrenia. *Society for Neuroscience meeting*. Atlanta, GA, Society for Neuroscience, 2006.

5. Brady, A. M., Bailey, A. M., **Calhoon, G. G.,** Logan, T. T., McGill, J. A., Ruiz, C. T., & Saul, R. D. (2007). Impaired executive function and learning set formation in the neonatal ventral hippocampal lesion model of schizophrenia. Program No. 607.11. *Society for Neuroscience meeting.* San Diego, CA: Society for Neuroscience, 2007.

6. John, C. E., **Calhoon, G. G.,** Obineme, C. G., & O'Donnell, P. (2007). Isolation rearing enhances prepulse inhibition deficits in a rat model of schizophrenia. Winter Conference on Brain Research, 2007.

7. John, C. E., **Calhoon, G. G.,** Obineme, C. G., & O'Donnell, P. (2008). Isolation rearing in rats with a neonatal ventral hippocampal lesion: A model of stress effects in schizophrenia. Program No. 761.25. *Society for Neuroscience meeting.* Washington DC: Society for Neuroscience 2008.

8. **Calhoon, G. G.,** Lewis, E., & O'Donnell, P. (2009). Limited dopamine contribution to hippocampal drive of up states in the limbic striatum. *Gordon Research Conference: Catecholamines*, University of New England, 2009.

9. Stalnaker, T. A., **Calhoon, G.,** Ogawa, M., Roesch, M. R., & Schoenbaum, G. (2009). Neural correlates of stimulus-response and response-outcome associations in dorsolateral versus dorsomedial striatum. Program No. 682.3. *Society for Neuroscience meeting.* Chicago, IL: Society for Neuroscience, 2009.

10. **Calhoon, G. G.,** Lewis, E., & O'Donnell, P. (2009). Dopamine involvement in hippocampal induced up states in the ventral striatum. Program No. 623.11. *Society for Neuroscience meeting.* Chicago, IL: Society for Neuroscience, 2009.

11. **Calhoon, G. G.,** John, C. E., & O'Donnell, P. (2010). Isolation rearing in rats with a neonatal ventral hippocampal lesion: A model of environmental effects in schizophrenia pathophysiology. *Schizophrenia International Research Society meeting.* Florence, Italy: 2nd SIRS Conference, 2010.

12. **Calhoon, G. G.** & O'Donnell, P. (2010). Prefrontal cortical inputs attenuate hippocampus-evoked responses in the limbic striatum. Program No. 552.1. *Society for Neuroscience meeting.* San Diego, CA: Society for Neuroscience, 2010.

13. Whitt, J. P., McDannald, M.A., **Calhoon, G. G.,** Karlsson, R.-M., O'Donnell, P., & Schoenbaum, G. (2010). Impaired reality testing in an animal model of schizophrenia. Program No. 707.10. *Society for Neuroscience meeting.* San Diego, CA: Society for Neuroscience, 2010.

14. **Calhoon, G. G.,** Shusterman, I., Gruber, A. J., Roesch, M. R., Schoenbaum, G., & O'Donnell, P. (2010). Cognitive inflexibility in rats with a neonatal ventral hippocampal lesion is associated with a disinhibited prefrontal cortex. Program No. 363.12. *Society for Neuroscience meeting.* San Diego, CA: Society for Neuroscience, 2010.

15. **Calhoon, G. G.** & O'Donnell, P. (2011). Cross-talk among inputs to the ventral striatum: Prefrontal cortical burst stimulation shunts hippocampal inputs. Program No. P39. *Winter Conference on Brain Research.* Keystone, CO: Winter Conference on Brain Research, 2011.

16. O'Donnell, P., Cabungcal, H. J., Piantadosi, P., Lewis, E., **Calhoon, G. G.**, Do, K. Q. (2011). Oxidative stress during development in prefrontal cortical interneurons in developmental animal models of schizophrenia. *Schizophrenia Bulletin* 37, suppl. 1, 111.

17. **Calhoon, G. G.** & O'Donnell, P. (2011). Burst prefrontal cortical stimulation reduces accumbens responses to hippocampal afferents. *Gordon Research Conference: Catecholamines*, Bates College, 2011.

18. Stalnaker, T.A., **Calhoon, G. G.**, Ogawa, M., Roesch, M. R., & Schoenbaum, G. (2011). Signaling of reward prediction errors by fast-firing interneurons in dorsomedial striatum is specific for the action that produced them. Program No. 512.12. *Society for Neuroscience meeting.* Washington, D.C.: Society for Neuroscience, 2011.

19. **Calhoon, G. G.** & O'Donnell, P. (2011). Robust prefrontal cortical activation suppresses synaptic responses in the limbic striatum. Program No. 655.13. *Society for Neuroscience meeting.* Washington, D.C.: Society for Neuroscience, 2011.

20. **Calhoon, G. G.** & O'Donnell, P. (2012). Prefrontal cortical modulation of synaptic responses via heterosynaptic inhibition in the ventral striatum. Program No. 99.05. *Federation of European Neuroscience Societies meeting.* Barcelona, Spain: FENS 2012.

21. **Calhoon, G. G.** & O'Donnell, P. (2012). Prefrontal cortical suppression of synaptic responses in the limbic striatum: The role of GABAergic inhibition. Program No. 335.09. *Society for Neuroscience meeting.* New Orleans, LA: Society for Neuroscience, 2012.

Professional Society Memberships

Society for Neuroscience (2005 – present)
American Association for the Advancement of Science (2010 – 2012)
Schizophrenia International Research Society (2010 – 2012)
Federation of European Neuroscience Societies (2012 – present)

Abstract

Title of Dissertation: The Nucleus Accumbens as a Switchboard: Heterosynaptic Suppression in the Ventral Striatum

Gwendolyn G. Calhoon, Doctor of Philosophy, 2013

Dissertation Directed by: Dr. Patricio O'Donnell, professor, Program in Neuroscience

Many brain circuits control behavior through the integration of information provided by separate inputs onto a common target neuron. Medium spiny neurons (MSNs) in the ventral striatum (VS) receive converging excitatory afferents from the prefrontal cortex (PFC), hippocampus (HP), and thalamus, among others, and the integration of these inputs is critical for shaping goal-directed behaviors. Although under baseline conditions the membrane activity of MSNs is controlled largely by the HP, the PFC can elicit up states in MSNs during periods of high frequency activity, such as that which occurs during decision making epochs. Moreover, during epochs of high PFC activity, the VS loses synchrony with the HP. It is therefore possible that PFC inputs locally attenuate responses to other glutamatergic inputs to the VS. We investigated whether strong, transient PFC activation can disengage the VS from the HP by measuring the effect of high frequency PFC stimulation on MSN responses to stimulation of other synaptic inputs. Using *in vivo* intracellular recordings, we found that delivering trains of stimuli to the PFC suppresses HP- and thalamus-evoked synaptic responses in the VS, partially through a GABAergic mediator. These findings indicate that high frequency PFC activity overrides HP control of MSN up state transitions, and provide evidence of heterosynaptic inhibition in this system *in vivo*. This interaction may enable the PFC to exert influence on basal ganglia loops during decision-making instances with minimal disturbance from ongoing contextual inputs.

The Nucleus Accumbens as a Switchboard:

Heterosynaptic Suppression in the Ventral Striatum

by
Gwendolyn Calhoon

Dissertation submitted to the faculty of the Graduate School
of the University of Maryland, Baltimore in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
2013

Table of Contents

List of Figures

Introduction

I. *The Basal Ganglia: An Overview*

The basal ganglia are a set of highly conserved forebrain nuclei that connect the cerebral cortex with behavior effector systems. In the primate brain, the basal ganglia include the caudate nucleus, putamen, and nucleus accumbens (NAc), which constitute the striatum, as well as the pallidum, subthalamic nucleus, and substantia nigra pars reticulata. Although the structural separation of the caudate and putamen by the internal capsule is absent in rodents (the caudate-putamen is the equivalent structure in rats), rat basal ganglia structures and the canonical circuits connecting them directly mirror the pattern of connectivity found in the primate (DeLong, 2000). Activity within these structures filters and enhances motor signals to shape action selection and behavioral output, but the cellular and synaptic mechanisms allowing this function are not completely understood.

Prototypical basal ganglia circuits can be parsed into the direct and indirect pathways (Figure 1), and originate in cortical and thalamic afferents to the striatum (Webster, 1961; McGeorge and Faull, 1989; Hontanilla *et al.*, 1994). Striatal projection neurons (medium spiny neurons; MSNs) within the direct pathway send their axons principally to the internal segment of the globus pallidus (GPi), which exerts tonic inhibition over the ventral lateral and parafasicular nuclei of the thalamus. As MSNs are GABAergic and typically silent, activation of these cells by cortical afferents results in the transient inhibition of the tonically active GPi, yielding disinhibition of the thalamus. The thalamus, thus activated, releases glutamate into the cerebral cortex (Graybiel, 1990), enhancing the original motor signal. The functional organization of the indirect circuit is

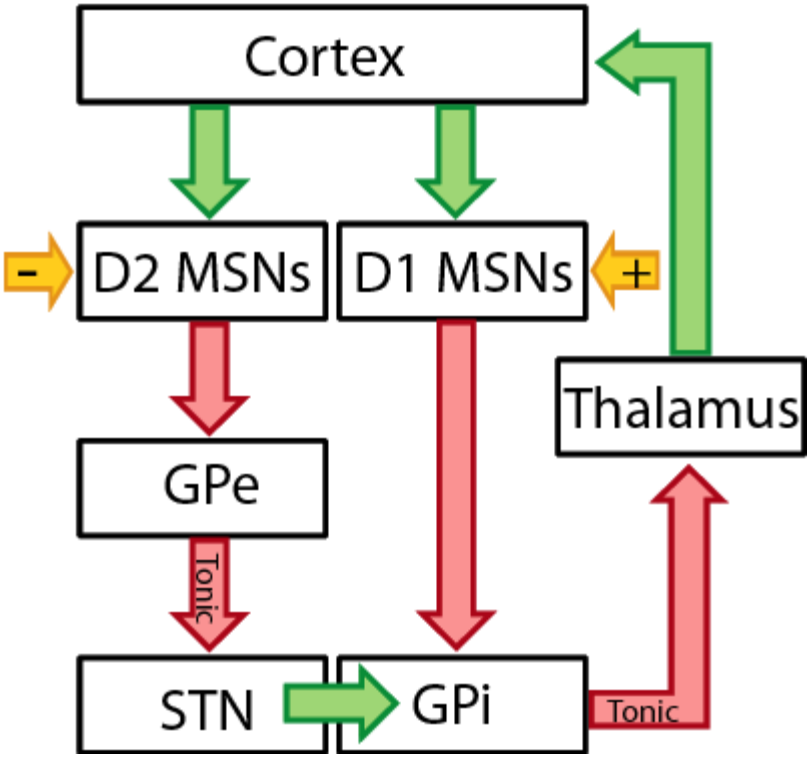

Figure 1. Basal Ganglia circuit diagram
In the canonical direct pathway (shown at left), cortical afferents excite D1-expressing MSNs in the striatum, which then inhibit tonically active GABAergic neurons in the internal segment of the globus pallidus (GPi), thus disinhibiting the thalamus leading to excitation in the cortex. In this pathway, dopamine (shown in yellow) excites MSNs through D1 receptors. In the indirect pathway (shown at right), cortical afferents excite D2-expressing MSNs in the striatum, leading to the disinhibition of the subthalamic nucleus (STN) by the external segment of the globus pallidus (GPe). The STN then transiently excites neurons in the GPi, leading to a reduction in thalamic and cortical activity. Dopamine (shown in yellow) inhibits MSNs through D2 receptors in the indirect pathway.

more complex than that of the direct circuit. Striatal MSNs within the indirect pathway target the external segment of the globus pallidus (GPe) and the subthalamic nucleus (STN). When activated by cortical afferents, indirect pathway MSNs inhibit GPe, resulting in disinhibition of STN. As the glutamatergic cells of the STN project rostrally to the GPi, their disinhibition promotes the downstream suppression of thalamic activity. This inhibition of the thalamus following indirect pathway activation stands in stark contrast to the outcome of direct pathway activation, and may provide counterbalanced regulation of basal ganglia output or inhibit undesired, antagonistic movement (Alexander and Crutcher, 1990). Alternatively, the role of the indirect pathway may be to terminate direct pathway activated movement (Smith et al., 1998). In any event, the outcome of basal ganglia function depends on adequate balance of activity in the direct and indirect pathways.

A. ***Basal Ganglia Inputs: Afferents to the Striatum***

1. ***Cortical Afferents***

The cerebral cortex provides critical afferent input to the striatum. In all mammals that have been studied, including rodents, carnivores, and primates, the striatum is innervated by sensory, motor, and association areas of the cortex (Kemp and Powell, 1970; Jones *et al.*, 1977; Oka, 1980; Veening *et al.*, 1980; Royce, 1982; Tanaka, 1987; McGeorge and Faull, 1989). Pyramidal neurons in layers III and V of the cerebral cortex provide the cortical input to the striatum (Kitai *et al.*, 1976b; Hedreen, 1977; Hedreen and McGrath, 1977; Schwab *et al.*, 1977; Wise and Jones, 1977; Veening *et al.*, 1980; Arikuni and Kubota, 1986), and produce two distinct types of corticostriatal

projections. Neurons in the pyramidal tract (PT) reside in the frontal cortex and project directly to motor neurons in the brain stem and spinal cord, sending collaterals to the striatum (Donoghue and Kitai, 1981; Landry *et al.*, 1984; Cowan and Wilson, 1994; Lei *et al.*, 2004). These collaterals form focal axonal arborizations in the striatum approximately 100-500 μm in diameter (Cowan and Wilson, 1994), and provide the striatum with a copy of the motor signal directly regulating movement; midbrain electrical stimulation of the PT evokes monosynaptic EPSPs in the striatum of intact rats (Wilson et al., 1982). Although PT afferents to the striatum form scattered focal terminations, this input is still substantial, as all pyramidals projecting to the brain stem send collaterals to the striatum (Cowan and Wilson, 1994; Levesque et al., 1996a; Levesque et al., 1996b; Levesque and Parent, 1998). By contrast, intertelencephalic (IT) pyramidal neurons form extensive bilateral corticocortical and corticostriatal connections. IT neurons innervate the striatum with sparse, distributed axonal arborizations that can spread more than 1 mm within the striatum (Wilson, 1987; Cowan and Wilson, 1994; Wright *et al.*, 2001).

The PT and IT inputs to the striatum are distinct in a number of ways (Wilson, 1987; Cowan and Wilson, 1994; Levesque *et al.*, 1996a; Levesque *et al.*, 1996b; Levesque and Parent, 1998; Reiner *et al.*, 2003; Parent and Parent, 2006). Whereas the IT afferents form contacts with contralateral cortex and striatum, the PT collateral to the striatum is restricted to the ipsilateral hemisphere. PT neurons possess relatively large somata located in deep layer V of cortex, whereas the relatively smaller IT neurons reside in superficial layer V and layer III of cortex. Moreover, the conduction velocity of axons arising from the PT pathway is three to four times more rapid than that of IT-type axons

(Wilson, 1986; Wilson, 1987; Bauswein *et al.*, 1989; Cowan and Wilson, 1994; Turner and DeLong, 2000). Unlike cortical neurons in the PT pathway, IT cells are exclusively activated by one aspect of a movement, with a response that is small in magnitude, but strongly directional (Bauswein et al., 1989; Turner and DeLong, 2000). Whereas both PT and IT frontal pyramidal neurons innervate the ipsilateral striatum, the distribution of their axons and synapticly evoked responses in this region differ markedly. These observations indicate that cortico-striatal projections are more complex than a simple excitatory glutamatergic relay.

Corticostriatal afferents synapse primarily on MSN spine heads, on which they form asymmetric contacts (Kemp and Powell, 1970; Somogyi *et al.*, 1981; Bouyer *et al.*, 1984). Quantification of corticostriatal contacts with MSNs revealed that 90% of cortical synapses localized to MSN spine heads, 5% localized to dendritic shafts, and the remaining 5% were found to be somatic (Xu et al., 1989). Inputs arising from the PT form slightly different synaptic contacts with MSNs than IT-type afferents; PT synapses are slightly larger compared to IT synapses (~0.9 µm versus ~0.5 µm terminal diameters, respectively), and the post synaptic density in PT corticostriatal synapses is generally perforated, whereas in IT corticostriatal synapses, it is not (Wright *et al.*, 1999; Wright *et al.*, 2001; Reiner *et al.*, 2003). The distinct profile of IT and PT synaptic contacts with MSNs has been used to demonstrate the preferential innervation of direct and indirect pathway MSNs by these two afferent streams (Lei et al., 2004). Direct pathway MSNs retrogradely labeled as striatonigral projection neurons and identified by their D1 receptor immunoreactivity (see below) primarily contain small, rounded spines in their dendritic arbors which resemble IT-receptive spines. By contrast, retrogradely labeled

striatopallidal MSNs in the indirect pathway immunoreactive for the D2 receptor contained notably larger spines resembling PT-receptive spines (Lei et al., 2004). The average terminal diameter of indirect pathway MSN spines was not as large as that of the PT afferent pathway, however, suggesting that indirect pathway MSNs receive a mix of PT and IT afferent innervation. It has been suggested that IT neurons provide the primary cortical input to both the direct and indirect populations of MSNs (Ballion et al., 2008).

The larger, more perforated synapses characteristic of PT connections in the striatum are more efficacious than synapses formed by the IT pathway. Indirect pathway MSNs receiving the majority of PT inputs possess a lower paired-pulse ratio and higher miniature excitatory postsynaptic current (mEPSC) frequency than direct pathway MSNs in a slice preparation (Kreitzer and Malenka, 2007; Cepeda *et al.*, 2008; Ding *et al.*, 2008). Moreover, indirect pathway MSNs tend to have higher basal firing rates than direct pathway MSNs (Mallet et al., 2006), and cortical stimulation preferentially induces immediate early gene expression in enkephalin immunoreactive indirect pathway MSNs (Berretta et al., 1997; Parthasarathy and Graybiel, 1997). These observations suggest that cortical input more effectively activates the indirect pathway than the direct, and emphasizes the importance of inhibitory control in neural processing within striatal circuits.

A high degree of convergence exists in the corticostriatal projection. Approximately 17,000,000 cortical pyramidal neurons innervate roughly 2,800,000 MSNs in the striatum, representing a 6:1 ratio of cortical cells to their striatal targets (Oorschot, 1996). The distributed pattern of cortical innervation within the striatum,

however, is such that corticostriatal projection neurons contact the maximal number of striatal neurons while making minimal contact with each postsynaptic cell (Zheng and Wilson, 2002). In fact, each corticostriatal projection neuron makes only a single or a few contacts with an individual MSN, and may only contact 1% of the neurons within its striatal axonal arborization. MSNs, for their part, receive convergent input from multiple corticostriatal cells, with the result that no two striatal neurons share entirely common cortical inputs.

Although this marked convergence exists within the striatum, the spatial relationships between cortical areas are maintained in their projections to this region (Webster, 1961; Kemp and Powell, 1970). For instance, prefrontal cortical areas preferentially project to the rostral caudate and nucleus accumbens, whereas the motor cortex projects to the rostral putamen (Kunzle, 1975). Furthermore, the somatotopy of the somatosensory and motor cortices is largely preserved in their projection to the dorsolateral striatum (Jones et al., 1977). The topography of corticostriatal projections is not strictly segregated, however, as overlap of inputs from interconnected cortical areas exists (Flaherty and Graybiel, 1991; Parthasarathy *et al.*, 1992; Flaherty and Graybiel, 1993). In fact, the convergence of inputs from multiple separate, but functionally related areas of cortex within the striatum is common (Brown et al., 1998; Hoffer and Alloway, 2001).

2. *Thalamic Afferents*

The thalamus provides dense, excitatory innervation to the striatum nearly the magnitude of the corticostriatal innervation, and has been under study for more than fifty

years (Cowan and Powell, 1956). The centromedian/parafascicular (CM/Pf) nuclei provide the main source of thalamostriatal input, with additional thalamic input to the striatum coming from the rostral intralaminar, midline, and specific relay nuclei (Smith and Parent, 1986; Berendse and Groenewegen, 1990; Fenelon *et al.*, 1991; Francois *et al.*, 1991; Sadikot *et al.*, 1992a; Sadikot *et al.*, 1992b; Deschenes *et al.*, 1995; Deschenes *et al.*, 1996a; Deschenes *et al.*, 1996b; Mengual *et al.*, 1999; McFarland and Haber, 2000; McFarland and Haber, 2001; Elena Erro *et al.*, 2002; McFarland and Haber, 2002; Smith *et al.*, 2004; Castle *et al.*, 2005; McHaffie *et al.*, 2005; Parent and Parent, 2005; Raju *et al.*, 2006; Lacey *et al.*, 2007; Smith *et al.*, 2009). These thalamic inputs are topographically arranged, with different elements of the thalamus innervating distinct regions of the striatum. The rostral most 1/3 of the Pf preferentially innervates the NAc, whereas the caudal 2/3 of the structure innervates the caudate, and dorsal Pf along with most of CM target the putamen. The remaining portion of CM projects to primary motor cortex (Smith *et al.*, 2004; Smith *et al.*, 2009). In rodents, the midline thalamic nuclei project to the ventral striatum, as well as parts of the dorsal striatum (Groenewegen and Berendse, 1994; Smith *et al.*, 2004; Smith *et al.*, 2009). In general, CM/Pf neurons send their primary axons to the striatum and collaterals to the cortex (Smith and Parent, 1986; Sadikot *et al.*, 1992b; Parent and Parent, 2005), which is the opposite relationship the majority of thalamic nuclei have with striatum and cortex. Although thalamic inputs to the striatum were historically thought to originate exclusively from non-specific nuclei, increasing evidence indicates that a large volume of this projection originates from specific relay nuclei (Smith *et al.*, 2004; Raju *et al.*, 2006). These projections are likely to provide a complex pattern of information to striatal loops.

In many ways, inputs to the striatum originating in the thalamus recapitulate the structural pattern of corticostriatal innervation. Thalamostriatal inputs form similar numbers of synapses on MSNs as those of cortical origin (Lacey et al., 2005; Raju et al., 2008), which are asymmetric in nature (Dube et al., 1988; Xu et al., 1989). Two isoforms of the vesicular glutamate transporter (VGluT) segregate with corticostriatal (VGluT1) and thalamostriatal (VGluT2) terminals, enabling the ready comparison of the distribution of synaptic contacts from these two sources onto MSNs (Lacey *et al.*, 2005; Raju *et al.*, 2006; Raju *et al.*, 2008; Doig *et al.*, 2010). Just as most corticostriatal synaptic contacts are on MSN spine heads, as many as 50 – 70% of the VGluT2 positive thalamic terminals in rats and monkeys form asymmetric synapses with MSN spines, with the remainder targeting dendritic shafts (Lacey *et al.*, 2005; Raju *et al.*, 2006; Raju *et al.*, 2008). Anterograde labeling studies have demonstrated that the centrolateral, mediodorsal, VA/VL, lateroposterior, anteroventral, and laterodorsal nuclei of the thalamus form more than 95% of their synaptic contacts on dendritic spines in the striatum (Raju et al., 2006). These synapses are closely apposed to dopamine boutons on spines, much as is the case with corticostriatal synapses (Smith and Bolam, 1990; Moss and Bolam, 2008). Considered separately from the entire population of thalamic inputs to the striatum, CM/Pf terminals preferentially innervate dendritic shafts of MSNs and interneurons (Dube *et al.*, 1988; Sadikot *et al.*, 1992b; Sidibe and Smith, 1996; Sidibe and Smith, 1999; Smith *et al.*, 2004; Raju *et al.*, 2006; Smith *et al.*, 2009). These synapses are not directly contacted by dopamine terminals (Smith et al., 1994), however that configuration does not eliminate them from receiving dopamine modulation as a result of volume transmission.

The role of thalamic input in striatal information processing is suggested by the inputs received by the thalamic nuclei innervating the striatum, which largely support attentional and orienting functions. The intralaminar thalamic nuclei receive inputs from various brainstem, cerebellar, and spinal cord nuclei, as well as the superior colliculus, pretectal nuclei, and the amygdala (McHaffie et al., 2005). These thalamic structures also receive input from the reticular formation, which specifically governs cortical arousal and attention (Kinomura *et al.*, 1996; Smith *et al.*, 2004; Minamimoto *et al.*, 2009; Smith *et al.*, 2009). Cerebellar input reaches the striatum through ventral anterior, ventral lateral (VA/VL), and rostral intralaminar thalamic nuclei (Hoshi et al., 2005). CM/Pf neurons receive the bulk of their synaptic inputs from GPi and SNr (Sidibe et al., 2002), and subsequently innervate functionally distinct territories of the striatum. In this way, these projections form segregated basal ganglia-thalamostriatal loops (Smith *et al.*, 2004; Smith *et al.*, 2009).

Activation of the monosynaptic glutamatergic thalamostriatal projection generates a somewhat complex pattern of responses in the striatum. CM/Pf stimulation in anesthetized cats and rats evokes short latency excitatory responses followed by inhibitory PSPs at longer latencies in MSNs and cholinergic interneurons (Kitai *et al.*, 1976a; Kocsis *et al.*, 1977; Vandermaelen and Kitai, 1980; Wilson *et al.*, 1983b; Wilson *et al.*, 1990). MSNs and cholinergic interneurons do not respond equivalently to thalamic stimulation. Trains of stimuli delivered to the CM produce increased firing in MSNs, but reduce firing in cholinergic interneurons (Nanda et al., 2009). Thalamic input to striatal cholinergic interneurons is particularly strong (Meredith and Wouterlood, 1990; Lapper and Bolam, 1992; Sidibe and Smith, 1999), and CM stimulation reduces ACh release in

the striatum (Zackheim and Abercrombie, 2005; Nanda *et al.*, 2009). In the behaving animal, thalamostriatal signals likely aid in learning of motivated behaviors, as CM/Pf cells respond most robustly to stimuli that are unpredictable or different from expectations (Minamimoto et al., 2005). On the whole, the thalamus appears to provide the striatum with information regarding attentional values, and may imbue the striatum with the ability to detect behaviorally significant events occurring on the contralateral side (Minamimoto and Kimura, 2002; Kimura *et al.*, 2004; Minamimoto *et al.*, 2005; Minamimoto *et al.*, 2009). The interaction among thalamic and other excitatory inputs to the striatum remains to be elucidated.

3. *Modulatory Input to the Striatum*

The striatum also receives substantial modulatory input from the midbrain. Dopamine terminals from the substantia nigra pars compacta and ventral tegmental area (VTA) synapse with MSNs (Arluison et al., 1984; Bouyer et al., 1984; Voorn et al., 1986) primarily on spine necks, however they occasionally also form synapses on dendritic shafts and rarely on MSN somata (Freund et al., 1984). These contacts are unlikely to be targeted; all striatal structures of the same size have an equal probability of contacting a DA axon (Moss and Bolam, 2008). Serotonin is released in the striatum from fibers originating in the raphe nucleus (Steinbusch et al., 1981). These modulatory projections are critical for striatal function and are involved in pathophysiological conditions resulting in basal ganglia dysfunction. The nature of this modulation will be reviewed below.

B. ***Basal Ganglia Output Structures***

From the striatum, MSNs project to the output nuclei of the basal ganglia, including the pallidum and substantia nigra (Grofova, 1975; Bunney and Aghajanian, 1976; Cuello and Paxinos, 1978; van der Kooy *et al.*, 1981; Haber and Nauta, 1983; Loopuijt and van der Kooy, 1985; Kawaguchi *et al.*, 1990; Bevan *et al.*, 1994). As stated above and schematized in Figure 1, MSNs of the direct pathway target the GPi and the GABAergic neurons of the SNr, and indirect pathway MSNs project to the GPe, which subsequently inhibits the STN. The GPe forms a recurrent GABAergic projection with the striatum (Staines *et al.*, 1981; Beckstead, 1983; Kita and Kitai, 1994; Bevan *et al.*, 1998), which specifically targets GABAergic interneurons (Staines and Fibiger, 1984; Bevan *et al.*, 1998). Furthermore, the STN makes sparse asymmetric contacts with striatal MSNs (Kita and Kitai, 1987). These reciprocal projections likely provide a pathway whereby information can be transferred between different functional domains of the basal ganglia, as described below.

Just as there is a high degree of convergence in the corticostriatal projection, there is a remarkable extent of convergence of MSN projection neurons onto their targets. There are approximately twenty nine times more striatal output neurons as there are pallidal and nigral target neurons put together (Oorschot, 1996). In the human brain, there are between 100 and 110 million MSNs bilaterally (Plenz and Wickens, 2010), which converge upon only 157,000 neurons in the GPi and 160,000 neurons in the SNr (Oorschot, 2010). The magnitude of convergence is similar in the rodent; approximately 5.6 million MSNs bilaterally (Oorschot, 1996) project to 6400 GPi neurons, 52,600 SNr neurons, and 27,200 STN neurons in the rat brain (Oorschot, 1996).

The basal ganglia impact the preparation of movements, the organization of cognition, and behavioral flexibility through their output to premotor and prefrontal cortices, and affect basic and innate motor activity through their output to brainstem nuclei like the superior colliculus and the reticular formation (Mink, 1996; Wise *et al.*, 1996; Redgrave *et al.*, 1999). As output structures of the basal ganglia, the SNr and GPi shape the movements of the eyes, head, and neck, as well as limb and axial movements, respectively, and impact upon motivated behaviors. SNr innervates the thalamus and targets the intralaminar nuclei, which project back to the striatum, as well as the ventromedial and medial dorsal thalamic nuclei, which in turn send an excitatory projection to the frontal cortex. The SNr also innervates the superior colliculus to influence eye movements, and the pedunculopontine nucleus, which plays a role in body-orienting movements (Beckstead, 1979; Gerfen *et al.*, 1982; Kita and Kitai, 1987; Nakanishi *et al.*, 1987; Deniau and Chevalier, 1992). The GPi also targets thalamic nuclei, namely the ventrolateral thalamus and the intralaminar/parafascicular nuclei, as well as the lateral habenula (LHb) (Nauta, 1974; Aghajanian and Wang, 1977; Herkenham and Nauta, 1977; Wang and Aghajanian, 1977). Following GPi activation, LHb regulates the activity of nigral and VTA dopamine neurons (Ji and Shepard, 2007; Matsumoto and Hikosaka, 2007), and in this way influences reward evaluation rather than motor execution alone (Hong and Hikosaka, 2008). Specifically, the GPi activation of LHb results in inhibition of SNc and VTA, signaling non-rewarding or disappointing outcomes (Hong and Hikosaka, 2008; Wickens, 2008).

C. *The Nucleus Accumbens: Input Structure to the Ventral Basal Ganglia*

The NAc is the centerpiece of the ventral striatum, and as such it is critical for cognition, decision-making and goal-directed behavior. Described as the limbic-motor interface (Mogenson et al., 1980), the NAc is situated at the confluence of cortical and limbic inputs, and as a basal ganglia structure, is poised to modulate motor output (Yang and Mogenson, 1987). The NAc receives prefrontal and orbitofrontal cortical inputs, as well as thalamic inputs, and also receives convergent afferents from limbic regions such as the hippocampus and amygdala (Groenewegen *et al.*, 1987; Groenewegen *et al.*, 1990; Groenewegen *et al.*, 1996; Mulder *et al.*, 1998). Stimulation of these limbic structures generates monosynaptic excitatory responses in NAc MSNs, often followed by more prolonged inhibitory responses (DeFrance and Yoshihara, 1975; Yim and Mogenson, 1982). Whereas prefrontal inputs target primarily distal dendrites in the ventral striatum, the hippocampal inputs to this region provide input to MSN proximal dendrites as well (Meredith et al., 1990), imbuing the hippocampus with notably strong control over the somatic membrane potential and firing of NAc MSNs (O'Donnell and Grace, 1995). NAc MSNs project principally to the ventral pallidum (VP)(Chang and Kitai, 1985), and transiently inhibit tonically active GABAergic neurons residing there (Yang and Mogenson, 1985; Chevalier and Deniau, 1990). As a result, the inhibition of the mediodorsal thalamus by the VP is transiently relieved, allowing the subsequent excitation of prefrontal cortex by the MD thalamus. Like their dorsal striatal counterparts, NAc MSNs share reciprocal projections with the ventral tegmental area (VTA) and the SNc (Chang and Kitai, 1985), and dopamine signaling in the NAc modulates MSN responses to glutamatergic inputs (Yim and Mogenson, 1982; Yang and

Mogenson, 1984; Yim and Mogenson, 1986; Yim and Mogenson, 1988). In addition, ventral striatal MSNs also project to basal forebrain cholinergic interneurons (Neigh-McCandless et al., 2002) in order to control distributed attentional processes (Sarter and Bruno, 2002). The NAc is a hub of information relevant to cognitive functions; elucidating the manner in which information is integrated in this region will significantly advance the field.

Although the striatum is canonically separated into ventral and dorsal parts (the NAc and the caudate-putamen, respectively), this sharp distinction is not functionally relevant. Immunohistochemical borders between these regions are hard to define, and the afferent and efferent connections formed with these areas of the striatum do not obey such borders (Voorn et al., 2004). A more appropriate separation of the striatum into functional domains on the basis of afferent projections has been proposed (Voorn et al., 2004), which describes the striatum as a continuum from the ventromedial to dorsolateral regions. To appreciate this organization, it is useful to consider the distribution of afferents to the NAc and dorsolateral striatum.

The cortical input to the NAc arises principally from the prefrontal cortex. The rodent prefrontal cortex can be divided into medial, lateral, and orbital parts with different subsections (Uylings and van Eden, 1990; Uylings *et al.*, 2003; Van De Werd and Uylings, 2008), each with their own pattern of striatal innervation. Within the striatum, prefrontal areas have a primary target, as well as extensive, less dense projections to neighboring striatal areas (Reep *et al.*, 2003; Haber *et al.*, 2006; Calzavara *et al.*, 2007). The rodent medial prefrontal cortex (mPFC), which receives input from the mediodorsal thalamus, includes infralimbic, prelimbic, anterior cingulate, and medial

agranular regions (Groenewegen, 1988; van Eden et al., 1990), and innervates the striatum with a ventromedial to dorsolateral topography (Berendse et al., 1992; Voorn et al., 2004). For instance, the most ventromedial area of mPFC, the infralimbic cortex, projects to the most ventromedial region of the striatum, the medial shell of the NAc. The infralimbic and prelimbic regions of mPFC preferentially project to extensive areas of rostral striatum, whereas the caudal striatum primarily receives medial agranular and anterior cingulate projections, however in all cases the ventromedial to dorsolateral organization is maintained. In addition to the mPFC, the lateral prefrontal cortex (lPFC) and orbital prefrontal cortex (OFC), which are subdivided into the dorsal and ventral agranular insular areas, and the medial, ventral, and lateral orbital areas, respectively (Haber *et al.*, 1995; Haber, 2003; Schilman *et al.*, 2008) also follow a topographical pattern of striatal innervation. OFC afferents to the striatum largely overlap with mPFC projections in the caudate-putamen, with the medial orbital projection completely within the prelimbic mPFC target (Berendse et al., 1992; Schilman et al., 2008). In addition to their overlapping innervation of the striatum, these prefrontal nuclei and the anterior cingulate also form strong interconnections through cortico-cortical projections (Vertes, 2004).

Ventromedial MSNs receive slightly different modulatory input than those residing in the dorsolateral striatum. For instance, the dopaminergic input to the ventromedial striatum is primarily of ventral tegemental area (VTA) origin, whereas the substantia nigra pars compacta provides dopamine to the dorsolateral striatum (Haber et al., 2000). Furthermore, serotonergic fibers are densest in the ventromedial striatum, including the all regions of the NAc and parts of the caudate, and norepinepherine from

the locus coeruleus targets the most medial regions of the striatum preferentially (Berridge et al., 1997). The spread of these modulatory inputs along ventromedial to dorsolateral gradients further support the notion of the striatum as a functional continuum.

The ventromedial striatum itself is classically divided into the NAc shell (more ventromedial) and core (more central) on the basis of different neuro- and immunochemical staining (Zaborszky *et al.*, 1985; Zahm and Brog, 1992; Groenewegen *et al.*, 1999), however this distinction is not entirely unambiguous. No marker fully distinguishes the shell from the core, however the shell lacks immunoreactivity for the Ca2+ binding protein calbindin D_{28K} (Graybiel and Ragsdale, 1978). Immunoreactivity for calbindin D_{28K} extends from the NAc core into and throughout the dorsal striatum, emphasizing the absence of definite borders between these structures.

The ventromedial striatum is of particular interest as a region rich in triadic relationships among its input structures. Such a relationship exists when two distinct nuclei innervating a single target nucleus are themselves interconnected. For instance, the midline paraventricular thalamic nucleus and the infralimbic and ventral prelimbic mPFC both innervate a restricted area of the striatum, namely the NAc shell and medial core, and moreover, the midline paraventricular nucleus projects to the mPFC as well (Berendse and Groenewegen, 1991; Berendse *et al.*, 1992; Groenewegen and Berendse, 1994). This type of triadic relationship has also been demonstrated to exit among the PFC, amygdala, and ventral striatum (McDonald, 1991), and can be inferred to exist among the PFC, ventral hippocampus, and ventromedial striatum (Groenewegen *et al.*, 1987; Jay and Witter, 1991; Cenquizca and Swanson, 2007). Triadic relationships may

be particularly important for supporting transfer of information across functional domains of the striatum, as described by Suzanne Haber and discussed below.

The general organization of striatal connections cannot be properly described with a dorsal/ventral dichotomy. It is more appropriate to group caudal and dorsolateral aspects of the rostral striatum due to their primary connection with motor and sensory cortical regions, versus ventral and medial aspects of the rostral striatum because of their dense connection with prefrontal cortical and limbic regions. This thesis will focus on physiological aspects of the manner in which ventral/medial striatal neurons integrate diverse sets of inputs.

II. *Cell Types and Transmitters in the Striatum*

The principal neuron of the striatum is the medium spiny neuron (MSN; (DiFiglia *et al.*, 1976; Wilson and Groves, 1980; Bishop *et al.*, 1982), which occupies upwards of 95 – 97% of the striatal neuronal population (Kemp and Powell, 1971a). MSNs are the primary cortical input target of the striatum (Somogyi et al., 1981), and its primary output neuron (Grofova, 1975). The remaining 3 – 5% of striatal neurons can be roughly divided into two groups, including the cholinergic interneurons (Bolam et al., 1984) and the GABAergic interneurons (DiFiglia *et al.*, 1976; Bishop *et al.*, 1982; Kita, 1993).

A. *Medium Spiny Neurons*

MSNs are readily identifiable based on their morphology, from which they derive their name. MSNs are characterized by medium sized somata 12-20 μm in diameter, from which radiate 5 – 10 moderately branched dendrites densely packed with spines

(DiFiglia *et al.*, 1976; Wilson and Groves, 1980; Bishop *et al.*, 1982; Chang and Kitai, 1982; Chang *et al.*, 1982; O'Donnell and Grace, 1993b). These dendrites branch once or twice into secondary and tertiary dendrites, and form roughly spherical arborizations that extend to a volume between 250 and 500 µm in diameter. Although the most proximal segment of the dendrite is smooth, spines begin approximately 20 µm from the soma and continue to the tip of each dendrite (DiFiglia et al., 1976; Wilson and Groves, 1980), where they reach an average density of 46 spines per 10 µm (Wilson, 1984). MSNs give rise to axons that project onward to the pallidum and substantia nigra, and also send recurrent collaterals within the striatum. These collaterals occupy roughly the same spread as the dendritic arbor of the parent neuron, however they can innervate as much as 1 mm in diameter of striatal tissue (Kawaguchi et al., 1990). MSN cytoarchitecture is consistent with the highly convergent nature of information processing in striatal circuits.

MSNs are GABAergic projection neurons that express dopamine receptors. All MSNs express the GABA synthetic enzyme glutamic acid decarboxylase (GAD), with particularly elevated levels of the GAD65 isoform (Kita and Kitai, 1988). Direct and indirect pathway MSNs can be differentiated based upon their expression of neuropeptides; direct pathway MSNs express substance P and dynorphin, whereas indirect pathway MSNs express enkephalin (Haber and Watson, 1983; Beckstead and Kersey, 1985; Gerfen and Young, 1988). Furthermore, D1 and D2 Receptors in the dorsal striatum segregate to direct and indirect pathway MSNs, respectively (Gerfen et al., 1990; Surmeier et al., 1996), although some overlap between the D1 and D2 populations exists, especially in the ventral striatum (Shuen et al., 2008). The pattern of cortical and thalamic innervation of the D1 and D2 populations of cells is similar, with

MSNs in both groups receiving convergent cortical and thalamic input, and individual cortical or thalamic afferents innervating D1 and D2 expressing MSNs (Doig et al., 2010).

The development of bacteria artificial chromosome (BAC) driven GFP labeling of the D1 and D2 populations of MSNs in mice (Heintz, 2001; Gong *et al.*, 2003) allowed for detailed characterization of these two classes of cells (Gertler et al., 2008). D1 MSNs tend to have greater total dendritic length and more branches than D2 MSNs (Gertler et al., 2008). *In vitro* recordings revealed that, whereas these two populations of MSNs possess similar inputs resistance, capacitance, time constant, and resting membrane potential (Kreitzer and Malenka, 2007; Cepeda *et al.*, 2008), striatopallidal D2-expressing MSNs tend to be more excitable than their D1-expressing counterparts. D2 positive MSNs respond to current injection with a higher degree of action potential firing (Kreitzer and Malenka, 2007), fire action potentials from a lower threshold (Cepeda et al., 2008), and exhibit a lower rheobase (Gertler et al., 2008) than D1 positive MSNs. Furthermore, back-propagating action potentials more reliably elevate cytosolic Ca2+ concentration at distal dendrites in D2 than in D1 MSNs (Day et al., 2008), indicating enhanced excitability of the dendrites of D2-expressing MSNs. This elevated excitability is likely due to the lesser dendritic volume of the D2 population, rendering these cells more electrotonically compact (Kreitzer and Malenka, 2007). D2 and D1 striatal MSNs may therefore differ in the manner in which they integrate their inputs.

MSNs exhibit characteristic electrophysiological properties that define the behavior of their membrane potentials. In the intact brain, MSNs transition between hyperpolarized resting potentials and more depolarized membrane potentials near firing

threshold, termed the down state and the up state, respectively. The presence of up and down states in dorsal striatal MSNs were initially revealed by intracellular recordings in immobilized rats (Wilson and Groves, 1981) and urethane anesthetized rats (Wilson et al., 1983a), in which the recorded cells were seen to fire in brief episodes separated by longer periods of quiescence. Up and down state transitions have subsequently been confirmed in dorsal and ventral striatal MSNs in the intact brain (O'Donnell and Grace, 1995; Wilson and Kawaguchi, 1996; Stern *et al.*, 1998). These transitions between up and down states are not intrinsic oscillations, but rather are glutamatergically driven by the cortex in dorsal striatum (Wilson *et al.*, 1983a; Kawaguchi *et al.*, 1989) and the hippocampus in the ventral striatum (O'Donnell and Grace, 1995). In fact, despite the abundance of NMDA and voltage gated currents in MSNs (Pennartz *et al.*, 1991; O'Donnell and Grace, 1993b; Cooper and White, 2000), up states are sustained by ongoing glutamatergic drive, as evidenced by the insensitivity of up state transitions to intracellular current injection (O'Donnell and Grace, 1995), the termination of up state transitions upon the termination of cortical input (Kasanetz et al., 2006), and computer modeling of MSN membrane activity (Wolf et al., 2005). Moreover, up state transitions in the ventral striatum in the anesthetized rat synchronize with local field potential events in the hippocampus, including spindles (Goto and O'Donnell, 2001b). The episodic firing pattern that emerges from up and down states in the anesthetized animal is also present in awake, behaving rodents (Schultz and Romo, 1988; Kimura *et al.*, 1990), in which it is associated with the initiation, execution, or termination of movement by the animal (Alexander, 1987; Schultz and Romo, 1988; Kimura *et al.*, 1990). However, the periodic state transitions observed in anesthetized animals most directly reflect events occurring

spontaneously during sleep (Mahon *et al.*, 2006). In awake animals, MSNs exhibit voltages within the range of up and down states, but state transitions are temporally disorganized and dependent upon activity in afferent structures; MSNs exhibit persistent epochs of membrane potential values in the range of up states when their inputs are active (Mahon *et al.*, 2006). Thus, studying the impact of afferent inputs on membrane potential states may contribute to understanding the manner in which MSNs integrate information.

The stable, hyperpolarized membrane potential of MSNs in the down state is dominated by an inward rectifying K+ current, I_{Kir} (Calabresi et al., 1987; Uchimura et al., 1989). I_{Kir} is voltage-sensitive and active at resting potential, but is blocked with membrane depolarization, resulting in a low input resistance and short time constant at rest that shunt excitatory currents and keep the cell at rest. When I_{Kir} closes following a barrage of glutamatergic inputs, the cell transitions into the up state and the input resistance and time constant of the membrane increase. These changes in turn enhance the spatial and temporal summation of excitatory responses in the MSN (Nisenbaum *et al.*, 1994; Nisenbaum and Wilson, 1995). Entering this more excitable state does not guarantee action potential firing, however, as most MSNs are silent in the up state (Wickens and Wilson, 1998), at least in part due to other K+ currents at work in these cells. In the slice, maintaining constant current near action potential threshold causes ramp depolarization and a long latency to spike in MSNs because of slowly inactivating A-type K+ channels, generating I_{As}. This K+ current competes with inward Na+ and Ca++ currents (Nisenbaum *et al.*, 1994; Nisenbaum and Wilson, 1995), but eventually inactivates following prolonged depolarization in the up state, which confers more excitability to the MSN.

The cerebral cortex and thalamus provide the primary glutamatergic input to dorsal striatal MSNs. MSNs respond to stimulation of these afferent structures with fast, monosynaptic, finely graded EPSPs, which likely represent the contribution of many small synaptic inputs (Wilson, 1986). In a slice preparation, MSN synaptic responses to cortical afferents appear to result from glutamate acting on non-NMDA receptors (Calabresi et al., 1996), however an NMDA component is observable in cortical and thalamic responses of MSNs *in vivo* (Kita, 1996). NMDA signaling also contributes to the onset of the up state, although NMDA receptor antagonism does not eliminate MSN up states (Kepecs and Raghavachari, 2007; Pomata et al., 2008).

In addition to excitatory inputs, local interactions also shape MSN electrical activity. MSNs are known to synapse with neighboring MSNs (Wilson and Groves, 1980; Somogyi *et al.*, 1981; Czubayko and Plenz, 2002; Tunstall *et al.*, 2002; Gustafson *et al.*, 2006). Contacts between pairs of MSNs through local collaterals are symmetrical with large vesicles (Wilson and Groves, 1980), and have been identified immunohistochemically with GAD and GABA staining (Aronin et al., 1986; Pasik et al., 1988). These synapses are located primarily on spine necks (50%) and dendritic shafts (40%), but are also rarely located on somata (10%; (Wilson and Groves, 1980), suggesting these MSN-MSN connections may exert lateral inhibition through dendritic processing (Plenz, 2003; Wilson, 2007). The probability of an MSN synapsing with another MSN is approximately 0.1 in the dorsal and ventral striata (Tunstall *et al.*, 2002; Koos *et al.*, 2004; Taverna *et al.*, 2004). These lateral inhibitory connections can also be bidirectional (Plenz and Wickens, 2010). MSN-MSN pairs form standard inhibitory synapses, which are of average conductivity, have fast rise and decay constants, few

multiple release sites, and average failure probability in the rat dorsal striatum (Koos *et al.*, 2004; Gustafson *et al.*, 2006) and ventral striatum (Taverna et al., 2004; Venance et al., 2004). The reversal potential at these synapses is between -60 and -45 mV, consistent with a $GABA_A$ response (Koos *et al.*, 2004; Bracci and Panzeri, 2006; Gustafson *et al.*, 2006). Electrical synapses between MSNs also exist in the striatum, especially in young animals. These have been demonstrated through Lucifer Yellow dye coupling in the NAc (Cepeda *et al.*, 1989; Walsh *et al.*, 1989; O'Donnell and Grace, 1993a; Onn and Grace, 1994) and paired whole cell patch recordings in rat slice (Czubayko and Plenz, 2002; Venance et al., 2004). The coupling coefficient for electrical synapses between MSNs is 3%. Lateral inhibition among MSNs has been suggested to map input strength differences into output differences (Fukai and Tanaka, 1997), to strengthen delayed or sequential inputs (Poggio and Reichardt, 1973), and to reduce the loss of information in the highly convergent striatopallidal and striatonigral projections (Oorschot, 2010). Direct MSN-MSN interactions can therefore occur both through GABAergic synapses and electrical coupling.

B. *Striatal Interneurons*

Another important contributor to MSN electrical activity is the population of local interneurons. Striatal interneurons do not send axonal projections to downstream structures, but rather shape the output of the striatum by modulating the activity of the MSNs. There are as many as nine morphologically distinct interneuron subtypes in the striatum that have been identified through Golgi staining (Chang et al., 1982), however only four distinct types have been established with neurochemical and

electrophysiological methods. These are separable into two main classes of interneurons, including three types of GABAergic interneurons and one type of cholinergic interneuron (Kawaguchi, 1993; Kawaguchi et al., 1995; Tepper and Bolam, 2004; Tepper et al., 2008). Unilaterally in the rat striatum, there are approximately 2,791,000 MSNs (Oorschot, 1996), 16,900 parvalbumin immunoreactive GABAergic interneurons (Luk and Sadikot, 2001), 21,300 somatostatin immunoreactive GABAergic interneurons (West et al., 1996), 13,200 calretinin immunoreactive GABAergic interneurons (Rymar et al., 2004), and 12,200 cholinergic interneurons (Oorschot, 2010), totaling approximately 2.85 million striatal neurons, of which only about 3% are interneurons (Rymar et al., 2004). Although they are greatly outnumbered by MSNs, striatal interneurons provide a critical influence over MSN activity.

Despite being in the minority, the GABAergic interneurons of the striatum produce disproportionately strong effects on MSNs (Koos and Tepper, 1999; Koos et al., 2004; Tepper et al., 2004), and play a key role in feed forward inhibition of the projection neurons. The GABAergic interneurons were first identified by their strong uptake of radiolabeled GABA (Bolam et al., 1983), and later by immunoreactivity for GABA and/or GAD (Bolam et al., 1985; Cowan et al., 1990; Kita, 1993). The best studied class of GABAergic interneurons is the fast spiking cells, which are identified by their expression of the calcium binding protein parvalbumin (Gerfen et al., 1985). PV interneurons constitute only about 0.7% of striatal neurons (Rymar et al., 2004), but have the strongest immunoreactivity for GAD67 and GABA in the striatum (Bolam et al., 1985; Cowan et al., 1990; Kita, 1993; Kubota et al., 1993). They are medium sized, with cell bodies 16-18 μm in diameter, and produce 5 – 8 aspiny, often varicose dendrites.

The dendrites extend into a sparsely branched arborization approximately 200-300 µm in diameter. An extremely dense, highly varicose axonal arborization arises from PV interneurons (in fact, the densest axonal arbor in the striatum), which overlaps and extends beyond the dendritic field. Within the striatum, PV interneurons exist in a dorsal to ventral, medial to lateral gradient (Luk and Sadikot, 2001).

Striatal PV interneurons receive a substantial monosynaptic excitatory input from the cortex; cortical afferents make multiple synaptic contacts with individual PV interneurons (Ramanathan et al., 2002). These contacts are principally formed through small, non-perforated terminals indicating the likely source of cortical input from the IT afferent stream (Kita, 1993; Kawaguchi *et al.*, 1995; Rudkin and Sadikot, 1999; Tepper *et al.*, 2004). This heavy pattern of innervation results in a greater responsivity to cortical stimulation among PV interneurons than MSNs, as revealed both by immediate early gene expression (Parthasarathy and Graybiel, 1997) and extracellular recordings *in vivo*, demonstrating that these cells fire repetitively and at a shorter latency to cortical stimulation than do MSNs (Kawaguchi et al., 1995; Mallet et al., 2005). These cells receive comparatively few thalamic inputs, however (Kita, 1993). PV interneurons also receive GABAergic input from the globus pallidus (Bevan et al., 1998), dopaminergic input from the substantia nigra and VTA (Kubota et al., 1987), and local cholinergic input (Chang and Kita, 1992). PV interneurons integrate these various inputs to inhibit MSNs, which they preferentially innervate at the soma or proximal dendrites (Kita *et al.*, 1990; Kita, 1993; Bennett and Bolam, 1994). As a consequence of their sensitivity to cortical input, PV interneurons are particularly effective in reducing the responsiveness of

MSNs to cortical stimulation (Koos and Tepper, 1999; Tepper *et al.*, 2004; Mallet *et al.*, 2005). Their role in affecting MSN responses to other inputs remains to be determined.

The electrophysiological profile of PV interneurons was first identified in young rats (Kawaguchi, 1993). The membrane properties of these cells are characterized by fast spiking, a nearly linear IV response, low input resistance, hyperpolarized resting potential, and narrow action potentials with rapid, large amplitude and brief duration after hyperpolarization (Koos and Tepper, 1999; Bracci *et al.*, 2002; Koos and Tepper, 2002; Bracci *et al.*, 2003; Taverna *et al.*, 2007). They have been noted to form gap junctions identifiable by electron microscopy (Kita *et al.*, 1990; Kita, 1993) and by paired recordings *in vitro* (Koos and Tepper, 1999). Coupling between PV interneurons is not strong enough to induce firing in paired cells, however paired cells display synchronized depolarization induced spiking.

PV interneurons are well poised to exert powerful feedforward inhibitory control over spike timing in large populations of MSNs. In striatal slices from adult rats, single spikes in individual fast spiking interneurons elicited unusually strong unitary IPSPs in neighboring MSNs, which were unidirectional and blocked by bicuculline (Koos and Tepper, 1999). Such strong, unidirectional relationships between PV interneurons and MSNs have been observed in up to 50% of tested pairs (Koos and Tepper, 1999; Koos and Tepper, 2002; Taverna *et al.*, 2007). The unitary IPSP caused by a single PV interneuron spike effectively delays depolarization induced spiking in MSNs, and bursts of action potentials in PV interneurons block MSN spiking entirely (Koos and Tepper, 1999). Although PV interneurons and MSN axon collaterals form biophysically similar synapses with MSNs, interneurons evoke larger amplitude, lower failure rate IPSP/Cs in

MSNs due to their more numerous, more proximal synaptic contacts than MSN collaterals (Koos et al., 2004). The feedforward inhibition exerted by fast spiking interneurons influences both direct and indirect pathway MSNs, however a slight preference for inhibition over direct pathway MSNs has been observed (Gittis et al., 2010).

The role of PV interneurons in striatal processing in the behaving animal is complex. Putative FSIs recorded from awake rats revealed increased firing during wakefulness, and entrained activity in this cell group during spindle activity when the animals were immobile. During performance in a radial arm maze task, putative PV interneurons did not show correlated firing (Berke, 2008). FSI phase locking with gamma oscillations in the ventral striatum have been observed, however, during reward epochs in foraging rats (Kalenscher et al., 2010), and FSI spiking increases upon initiation of choice in a simple choice task (Gage et al., 2010). It is possible that feed forward inhibition of MSNs is mediated by cells with different firing rates and behavioral correlates.

A second class of GABAergic interneurons in the striatum is identified by somatostatin (SOM) immunoreactivity. This same neuronal population also expresses neuropeptide Y, NADPH-diaphorase, and nitric oxide synthase (NOS; (Vincent and Johansson, 1983; Chesselet and Graybiel, 1986), although only 73% of these cells express all four peptides (Figueredo-Cardenas et al., 1996). Because of the variability in immunoreactivity among this population of cells, it is difficult to determine exactly what proportion of striatal neurons fall into this class, however it is estimated that SOM interneurons occupy approximately 0.55 – 0.7% of striatal neurons. SOM cells are also

strongly immunopositive for GAD67 (Kubota et al., 1993), and their boutons are GABA positive (Kubota and Kawaguchi, 2000). The cell bodies of SOM cells are 15-20 µm across with 2 – 5 thick, aspiny dendrites with few branches extending 600 µm in diameter (DiFiglia and Aronin, 1982; Vincent and Johansson, 1983; Vincent *et al.*, 1983; Aoki and Pickel, 1988; Kawaguchi, 1993). SOM interneurons give rise to one or two sparse axons, which course in straight lines up to 1 mm (Kawaguchi, 1993).

SOM interneurons receive similar inputs as PV FSIs, including glutamate from the cortex (Kawaguchi, 1993), dopamine from the midbrain (Kubota et al., 1988; Li et al., 2002), GABA from the GP (Bevan et al., 1998), and acetylcholine from local striatal interneurons (Vuillet et al., 1992). These cells are characterized by low threshold Ca2+ spikes (LTS) elicited by current injection or synaptic stimulation, as well as plateau potentials (P) following current injection or especially strong synaptic stimulation, leading to their designation as "PLTS" interneurons (Kawaguchi, 1993). PLTS interneurons have a markedly high input resistance (>600 MΩ), and relatively depolarized resting membrane potentials. Comparable to PV interneurons, PLTS interneurons fire long duration action potentials (Kawaguchi, 1993; Kubota and Kawaguchi, 2000; Centonze *et al.*, 2002). Each PLTS interneuron makes one or limited contacts with individual MSNs on dendritic shafts and spines (Takagi et al., 1983), as is evidenced by the extremely low variability in IPSC amplitude elicited by PLTS spikes (Tepper and Bolam, 2004; Tepper et al., 2008). These cells are not spontaneously active *in vivo*, and their role in striatal processing is not yet well understood.

The third accepted class of GABAergic interneurons in the striatum has received very little study to date, and its electrophysiological profile has not been established.

Calretinin immunoreactive interneurons have been identified histologically, with medium sized cell bodies (12 – 20 μm) and a few smooth, aspiny dendrites (Bennett and Bolam, 1993). CR interneurons make up approximately 0.8% of the neuronal population in the rat striatum (Rymar et al., 2004). In primates, however, the proportion of CR interneurons is greater, such that they outnumber PV and SOM/NPY neurons 3 or 4:1 (Wu and Parent, 2000).

The striatum has one of the highest levels of acetylcholine in the brain, which is provided endogenously by cholinergic interneurons (Mesulam *et al.*, 1992; Contant *et al.*, 1996). Cholinergic interneurons represent between 1 and 2% of all neurons in the mammalian striatum (Kemp and Powell, 1971b; Bolam *et al.*, 1984; Phelps *et al.*, 1985). This population of interneurons was first identified in the striatum because of their large cell bodies (Goldberg and Wilson, 2010), which can be in excess of 50 μm in diameter. These cells give rise to 2 – 4 aspiny dendrites which branch densely and profusely to cover approximately 1 mm of striatal tissue, as well as a fine extensive axon which arises from a primary dendrite and can innervate a 2 mm area in the striatum (Chang and Kitai, 1982; Bolam *et al.*, 1984; DiFiglia and Carey, 1986; DiFiglia, 1987; Wilson *et al.*, 1990; Kawaguchi, 1992; Kawaguchi, 1993).

The electrophysiological profile of cholinergic interneurons is one of intrinsic, ongoing activity. *In vivo* intracellular recordings reveal that these cells are spontaneously active, maintaining tonic firing between 3 and 10 Hz even in ipsilateral decorticated animals (Bishop et al., 1982; Wilson et al., 1990). As tonically active neurons (TANs), many of the cholinergic interneurons evidence ongoing tonic firing in *in vitro* slice preparations, in which these cells have been separated from their inputs (Jiang and North,

1991). This spontaneous activity is autonomous; it is insensitive to blockade of AMPA, NMDA, $GABA_A$, muscarinic Ach, and dopaminergic receptors (Bennett and Wilson, 1999), and is primarily due to a robust persistent Na+ current repeatedly bringing cholinergic interneurons to action potential threshold (Maurice et al., 2004). In addition to tonic firing, TANs also engage in rhythmic bursting, subthreshold oscillations, and irregular firing (Bennett and Wilson, 1999; Wilson, 2005).

Striatal cholinergic interneurons receive afferent input from both distal and local sources. These cells receive monosynaptic glutamatergic input from the cortex and the intralaminar nuclei of the thalamus. Cortical afferents synapse principally on the distal dendrites of TANs, whereas thalamic afferents, by contrast, synapse on proximal dendrites and somata as well (Wilson *et al.*, 1990; Lapper and Bolam, 1992; Kawaguchi, 1993; Bennett and Wilson, 1998; Thomas *et al.*, 2000). Cholinergic interneurons receive GABAergic input from striatal interneurons (Sullivan et al., 2008) through $GABA_A$ receptors (Chang and Kitai, 1982; DiFiglia and Carey, 1986; DiFiglia, 1987; Bennett and Wilson, 1998). Because these cells are tonically active, ionotropic signaling in cholinergic interneurons simply advances or delays the next action potential (Bennett and Wilson, 1998). Long lasting metabotropic signaling may make more of an impact on TAN activity. For instance, muscarine and other muscarinic agonists effectively silence TANs, as does focal stimulation of striatal slices, via M_2 class receptors (Calabresi *et al.*, 1998; Bonsi *et al.*, 2008).

The direct effect on MSNs by cholinergic interneuron signaling is excitatory in nature. Cholinergic interneurons form the majority of their synapses (45%) with MSN dendritic shafts, however they also target spine necks (34%) and somata (20%; (Izzo and

Bolam, 1988). MSNs express M1 and M4 muscarinic receptors (Bernard et al., 1992; Hersch et al., 1994; Yan et al., 2001), through which ACh induces inward current by suppressing K+ currents (Akins *et al.*, 1990; Kitai and Surmeier, 1993; Hsu *et al.*, 1996; Gabel and Nisenbaum, 1999; Galarraga *et al.*, 1999; Shen *et al.*, 2005; Shen *et al.*, 2007). ACh action at muscarinic receptors also downregulates Ca_v1 and Ca_v2 currents in MSNs through M4 receptors (Howe and Surmeier, 1995; Perez-Rosello et al., 2005), and as these currents are coupled to calcium activated K+ currents (Vilchis et al., 2000), this action increases the excitability of MSNs. Furthermore, M1 receptor activation elevates MSN excitability by reducing Kv4 channel activity (Akins et al., 1990) via protein kinase C signaling (Nakamura et al., 1997). This net increase in MSN excitability by the direct action of cholinergic interneurons is evident in reduced AHPs and increased evoked firing rate in a slice preparation (Perez-Rosello et al., 2005).

Cholinergic interneurons also innervate the GABAergic interneurons of the striatum, through which they exert opposing effects on MSNs. ACh acts through nicotinic receptors on FSIs, resulting in their depolarization and firing (Koos and Tepper, 2002), which subsequently leads to the inhibition of MSNs. This indirect inhibition of MSNs by cholinergic interneurons is diminished somewhat inasmuch as ACh activates presynaptic muscarinic receptors to reduce GABA release from the FSIs (Koos and Tepper, 2002; Perez-Rosello et al., 2005), however this same presynaptic suppression of release via muscarinic receptors acts on glutamatergic afferents to reduce excitatory signaling in MSNs (Akaike et al., 1988; Barral et al., 1999).

In the awake behaving primate, cholinergic interneurons can be identified by their tonic activity. These TANs share the same striatal spatial distribution as choline acetyl

transferase immunoreactive interneurons (Aosaki et al., 1995), suggesting the populations are the same or overlap. Upon presentation of a primary reward, TAN firing pauses for a few hundred milliseconds (Kimura *et al.*, 1984; Apicella *et al.*, 1997). Furthermore, TANs acquire a pause in firing to unconditioned stimuli that predict reward which is lost during extinction of the association (Aosaki et al., 1994). The pause in TAN firing signals the motivational significance not only of rewarding stimuli, but for aversive stimuli as well (Ravel *et al.*, 1999; Apicella, 2002; Morris *et al.*, 2004), and may result from feed forward inhibition mediated by striatal GABAergic interneurons.

Although they constitute a small proportion of the striatal neuronal population, interneurons exert a strong influence over striatal function. Among the diverse population of striatal interneurons, PV-positive fast-spiking interneurons stand out as being heavily modulated by afferent inputs and having a strong impact on MSN firing. The feed-forward inhibitory mechanisms their connectivity allows are only now beginning to be explored.

C. *Dopamine Signaling in the Striatum*

Dopamine is essential for all forms of striatal function; and in particular, is critically important for habit learning and the generation of movement (Albin *et al.*, 1989; Wickens *et al.*, 2003; Schultz, 2006). In the canonical model of dopamine function in the striatum, dopamine enhances activity in direct pathway MSNs through D1-like receptors, and inhibits activity in indirect pathway MSNs through higher affinity D2-like receptors (Albin et al., 1989). In the original conception of this "classical" model, dopamine's effects were thought to be acute and readily reversible (Albin et al., 1989). Although this

canonical action of dopamine in the striatum has been largely confirmed, dopamine has also been found to have persisting effects on striatal processing.

Dopamine in the striatum is released from fibers originating in the substantia nigra pars compacta or ventral tegmental area (Anden et al., 1964) and acts on dopamine receptors on MSNs and interneurons. Dopaminergic inputs to striatal MSNs precisely converge with glutamatergic inputs; in the NAc, dopaminergic terminals innervate MSNs targeted by hippocampal inputs (Totterdell and Smith, 1989), often on the same spine (Sesack and Pickel, 1990). This pattern of dopamine modulation of MSN responses to glutamatergic inputs at the level of the spine is maintained for prefrontal cortical (Sesack and Pickel, 1992) and amygdalar (Johnson et al., 1994) inputs.

Dopamine signaling through D1 receptors can promote or inhibit MSN excitability. Striatonigral, direct pathway MSNs express D1 receptors (Gerfen et al., 1990; Surmeier et al., 1996), which are positively coupled to adenylyl cyclase (AC) through G_{olf} (Herve et al., 1995). Dopamine signaling through D1 causes the activation of protein kinase A (PKA) through cAMP (Svenningsson et al., 2004), which subsequently enhances surface expression of AMPA and NMDA receptors (Snyder *et al.*, 2000; Hallett *et al.*, 2006). More acutely, PKA phosphorylation of the NR1 subunit of the NMDA receptor enhances currents through this receptor channel (Cepeda *et al.*, 1993; Blank *et al.*, 1997). Despite their primary excitatory effects, D1-family receptors can also reinforce quiescence in MSNs in the down state. D1 signaling reduces Na+ channel availability without changing the voltage dependence of fast activation or inactivation (Surmeier et al., 1992). PKA phosphorylation of the pore forming subunit of the Na+ channel promotes the entry of the channel into a non-conducting, slow inactivated state

(Carr et al., 2003), which can only be reversed by hyperpolarization. For MSNs in the up state, however, D1 stimulation elevates responsiveness to intrasomatic current injection (Hernandez-Lopez et al., 1997). This increase in excitability is due to enhanced opening of L-type Ca2+ channels following phosphorylation by PKA (Surmeier *et al.*, 1995; Gao *et al.*, 1997), as well as enhanced opening of NMDA receptors (Cepeda *et al.*, 1993; Levine *et al.*, 1996; Snyder *et al.*, 1998; Flores-Hernandez *et al.*, 2002). Moreover, dopamine can contribute to drive MSNs into the upstate through these D1-mediated effects on Ca2+ channels and NMDA receptors in corticostriatal slices (Vergara et al., 2003). MSNs in co-cultures of cortex and striatum do not possess up states (Tseng et al., 2007) unless dopamine neurons are added to the culture (Plenz and Kitai, 1998; Tseng et al., 2007). The ability of dopamine to influence MSN transitions into the up state is further evidenced by the ability of burst like VTA stimulation to induce up states in MSNs in the anesthetized rat (Goto and O'Donnell, 2001a). The amplitude (West and Grace, 2002) and duration (Goto and O'Donnell, 2001a) of MSN up states in the intact brain are sensitive to D1 receptor antagonism. In these ways, dopamine signaling through D1 receptors enhances MSN responses to sustained glutamatergic inputs, whereas it diminishes MSN responses to weak glutamatergic inputs coincident with MSN down states.

Dopamine effects mediated by D2-family receptors are principally inhibitory. Striatopallidal, indirect pathway MSNs express D2-family receptors, which couple to $G_{i/o}$ to inhibit adenylyl cyclase through the $G_{\alpha 1}$ subunit (Stoof and Kebabian, 1984). What is more, the $G_{\beta\gamma}$ subunit decreases Cav2 Ca2+ channel opening, generates diacylclycerol (DAG), activates protein kinase C, liberates inositoltriphosphate, and mobilizes

intracellular Ca2+ stores (Nishi *et al.*, 1997; Hernandez-Lopez *et al.*, 2000), all to inhibitory effect. D2 receptor activation reduces MSN AMPA currents (Cepeda et al., 1993) and promotes AMPA receptor trafficking out of the cell membrane (Hakansson et al., 2006), decreasing cell responsiveness to excitatory synaptic inputs. Furthermore, D2 receptor activation reduces opening of voltage gated Na+ channels (Surmeier et al., 1992) and promotes the opening of K+ channels (Greif et al., 1995) to sustain the resting potential. Even when MSNs are held at up state membrane potentials in striatal slices, D2 receptor agonists reduce the responsiveness of these cells to stimulation of cortical afferents (Hernandez-Lopez et al., 2000). This inhibitory effect is due in part to the reduction of presynaptic neurotransmitter release via D2 activation (Calabresi *et al.*, 1992a; O'Donnell and Grace, 1994; Hsu *et al.*, 1995; Flores-Hernandez *et al.*, 1997; Cepeda *et al.*, 2001; Bamford *et al.*, 2004), either through direct activation of receptors in cortical terminals (O'Donnell and Grace, 1994) or through retrograde endocannabinoid signaling (Yin and Lovinger, 2006).

Most, if not all, striatal interneurons express dopamine receptors (Tepper et al., 2004). For instance, dopamine signaling through D2 receptors on cholinergic interneurons diminishes ACh release by reducing autonomous spiking and inhibiting Ca2+ entry, which is necessary for exocytosis (Maurice et al., 2004; Salgado et al., 2005). This D2-mediated inhibition may serve a homeostatic function on ACh signaling, as dopamine terminals express nicotinic ACh receptors (Zhou et al., 2002). GABAergic interneurons in the striatum tend to be enriched with D1-like D5 receptors (Rivera et al., 2002), which enhance activity in these cells through stimulation of adenylyl cyclase (Hartman and Civelli, 1997).

The opposing effects of dopamine on direct and indirect pathway MSNs in the striatum suggest opposing roles of these two pathways in supporting movement. As described above, the outcome of direct basal ganglia pathway activity is to increase thalamic activity, and subsequently excite the cortex, whereas indirect basal ganglia pathway activity results in reduced thalamic and cortical activity. Computer modeling suggests that indirect pathway targets such as the GPe and STN would normally adopt synchronous rhythmic bursting patterns were it not for the inhibitory effect of striatopallidal MSNs over these structures (Terman et al., 2002). In fact, in individuals suffering from Parkinson's Disease, this anomalous activity in GPe and STN is present, and silencing these structures with lesions or deep brain stimulation reduces motor symptoms (Gross et al., 1999; Hutchison et al., 2004). It has been suggested that striatonigral MSN activity normally functions to promote action, whereas striatopallidal MSN activity suppresses action (Mink, 2003). In this model, dopamine functions to enhance motor activity by supporting direct pathway activity and inhibiting indirect pathway activity when necessary.

D. *Endocannabinoid Signaling in the Striatum*

Endocannabinoids are lipid based retrograde transmitters which act through the g-protein coupled CB1 receptor in the brain to critically regulate neural activity. The CB1 receptor is highly expressed throughout the extended striatum in discrete neuronal populations (Herkenham et al., 1991) in a dorsolateral to ventromedial gradient in which the density of CB1 receptors is comparatively lower in the NAc (Herkenham *et al.*, 1990; Herkenham *et al.*, 1991; Jansen *et al.*, 1992). Double labeling *in situ* hybridization

histochemistry has revealed that PV positive, GAD67-containing interneurons express CB1 mRNA, but cholinergic interneurons, calretinin-containing, and somatostatin-containing interneurons do not (Marsicano and Lutz, 1999; Hohmann and Herkenham, 2000; Martin *et al.*, 2008). The striatonigral and striatopallidal populations of MSNs both express CB1 (Tsou *et al.*, 1998; Hohmann and Herkenham, 2000; Julian *et al.*, 2003; Martin *et al.*, 2008), but expression is higher in direct pathway, striatonigral MSNs (Martin et al., 2008).

Endocannabinoids are synthesized on demand in postsynaptic neurons to reduce presynaptic release of fast acting neurotransmitters. In slice preparations of dorsal striatal tissue, CB1 agonists inhibit GABAergic (Szabo *et al.*, 1998; Hoffman and Lupica, 2001; Centonze *et al.*, 2004; Adermark and Lovinger, 2007a; Adermark and Lovinger, 2007b; Uchigashima *et al.*, 2007) and glutamatergic (Gerdeman and Lovinger, 2001; Hoffman and Lupica, 2001; Huang et al., 2001; Robbe et al., 2001) synaptic transmission onto MSNs. These findings also hold true in the NAc (Hoffman and Lupica, 2001; Robbe et al., 2001). In the awake animal, signaling through CB1 receptors has been implicated in reward and addiction (Casadio *et al.*, 1999; Cossu *et al.*, 2001; De Vries *et al.*, 2001; Di Marzo *et al.*, 2001; Gerdeman *et al.*, 2003; Wang *et al.*, 2003; Sanchis-Segura *et al.*, 2004; Houchi *et al.*, 2005; Caille *et al.*, 2007; Hansson *et al.*, 2007) and is necessary for habit formation (Hilario et al., 2007).

E. *NO Signaling in the Striatum*

Nitric oxide (NO) is a gaseous neuromodulator that regulates physiological processes in the periphery and the brain (Garthwaite, 2008). Three forms of the nitric

oxide synthatse (NOS), the enzyme responsible for synthesizing NO, have been identified, including neuronal (nNOS), inducible (iNOS), and endothelial (eNOS; (Alderton et al., 2001; Garthwaite, 2008). nNOS is activated by calcium/calmodulin, uses NADPH as an electron donor (Bredt and Snyder, 1990; Mayer et al., 1990; Schmidt and Murad, 1991), and is expressed in moderate levels in basal ganglia nuclei (Bredt et al., 1990; Vincent, 1994). One class of striatal GABAergic interneurons can be identified as NOS expressing (see above) using NADPH-diaphorase histochemical or nNOS immunocytochemical staining techniques (Hope *et al.*, 1991; Kawaguchi, 1993; Gracy and Pickel, 1997). NO released from these cells modulates MSN activity through signal transduction mechanisms common for NO in the brain (Murad, 2006; Garthwaite, 2008), principally via activation of soluable guanylyl cyclase (sGC) and production of the second messenger cGMP (Calabresi et al., 1999a; Calabresi et al., 1999b; West and Grace, 2004).

The importance of NO signaling in the striatum is underscored by the abundance of NO signal transduction molecules in this region. sGC activity is higher in the striatum than in any other part of the brain (Hofmann et al., 1977; Matsuoka et al., 1992). The sGC signaling cascade is localized postsynaptically in MSNs relative to the presynaptic sources of NO in striatal interneurons (Calabresi *et al.*, 1999b; Sancesario *et al.*, 2000; Hidaka and Totterdell, 2001; French *et al.*, 2005). sGC and cGMP activated by NO subsequently activates cGMP-dependent protein kinase (PKG), which increases DARPP-32 in MSNs to regulate long term changes in synaptic efficacy (Calabresi et al., 2007). NO also inhibits phosphodiesterase (PDE) to increase membrane excitability and responsiveness to cortical input in MSNs (West and Grace, 2004; Threlfell *et al.*, 2009).

Furthermore, NO facilitates intracellular calcium release from mitochondrial pools in striatal neurons (Meini *et al.*, 2000; Horn *et al.*, 2002).

The efflux of NO from striatal interneurons is highly influenced by the activity of classical neurotransmitters. Glutamate signaling through NMDA receptors on NOS interneurons causes the activation of nNOS by phosphoryllation of ser1412 (Rameau et al., 2007) by way of Akt activation. Moreover, NMDAR/nNOS-dependent striatal NO efflux is robustly increased *in vivo* by electrical stimulation of frontal cortical afferents (Sammut et al., 2007). Dopamine signaling through D1/5 receptors also stimulates NOS interneurons to release NO (Centonze et al., 2002; Centonze et al., 2003).

Overall, striatal NO efflux acts to enhance excitatory transmission in MSNs. Once released, NO can inhibit glutamate transporters, resulting in increased extracellular glutamate concentrations (Lonart and Johnson, 1994; Pogun et al., 1994; Taskiran et al., 2003). Furthermore, push-pull perfusion techniques have demonstrated that local infusion of NO generators increase glutamate release in the dorsal striatum (Segovia et al., 1994) and the NAc (Kraus and Prast, 2002). Exogenous application of NO facilitates glutamate release in the NAc resulting from electrical stimulation of the fimbria (Kraus and Prast, 2001; Kraus and Prast, 2002). In addition to facilitating glutamate release in the striatum, NO also enhances the release of modulatory neurotransmitters. Endogenous NO efflux (stimulated by intrastriatal infusion of nNOS substrates such as L-arginine or NG-hydroxy-L-arginine) facilitates DA release *in vitro* (Zhu and Luo, 1992; Chaparro-Huerta *et al.*, 1997; Liang and Kaufman, 1998) and *in vivo* (Strasser *et al.*, 1994; Spatz *et al.*, 1995; West and Galloway, 1997b; West and Galloway, 1997a). In awake and anesthetized rats, NO generators (such as diethylamine/NO, SNAP, and 3-

morpholinosyolnonimine (SIN-1)) infused into the NAc enhances release of ACh (Prast *et al.*, 1995; Prast *et al.*, 1998; Kraus and Prast, 2001).

Release of NO in the striatum follows both tonic and phasic patterns, and these two patterns of release support divergent functions in MSNs. The application of the NO scavenger carboxy PT-10 *in vivo* reduces MSN up states and EPSP amplitude, indicating that tonic NO signaling normally acts to enhance membrane activity (West and Grace, 2004). The role of phasic NO signaling is a matter of some contention, however; acute NO efflux may facilitate (West *et al.*, 2002; Liu *et al.*, 2005) or inhibit (Di Giovanni et al., 2003; Galati et al., 2008) MSN membrane activity. NO activity surely mediates electrotonic coupling and synchrony between MSNs, however, as nNOS inhibition alters oscillatory activity within striatopallidal circuits (West, 2010), and NO efflux evoked by corticostriatal train stimulation facilitates dye-coupling between MSNs (O'Donnell and Grace, 1997).

III. *Physiology and Network Integration in the Striatum*

Medium spiny neurons in the striatum must integrate diverse and multitudinous points of incoming information to influence target structure activity and shape learning and behavior. The converging cortical, thalamic, and limbic inputs to the striatum determine functional domains within the structure, which act both as parallel and integrative circuits. The high degree of convergence in the striatum presents a challenge for retaining the specificity of signals transmitted onward in the basal ganglia, which the striatum answers using a combinatorial, ensemble approach, as well as gating and non-linear summation. Striatal network integration and physiology are considered here.

A. *Combinatorial Coding*

The pattern of connectivity within the striatum renders individual MSNs as sensitive detectors of activity in a particular set of corticostriatal neurons. Each MSN receives approximately 5000 synapses of cortical origin (Kincaid et al., 1998), so that in the striatum as a whole, integrative, combinatorial networks emerge to produce functional domains. The topography of the striatum relative to the body is organized such that information arising different body parts is kept separate, and within the resulting somatotopic framework, there is overlap of information arising from different sensory modalities (Malach and Graybiel, 1986; Flaherty and Graybiel, 1991). Because of this organization, sensory stimulation results in extensive and patchy activity in the striatum (Brown and Sharp, 1995). This pattern of innervation allows individual MSNs to monitor activity among a set of cortical projection neurons in a cell assembly (O'Donnell *et al.*, 1999) or synfire chain (Abeles et al., 1993; Prut et al., 1998) that may represent a particular situation, action, or combination of situation and action.

The distribution of cortical synapses in the striatum results in largely non-overlapping patterns of input to each MSN. Because the interval between synaptic boutons on a corticostriatal axon has a Poisson distribution with a mean of 10 μm spaces (Kincaid et al., 1998), and because the spread of cortical axons in the striatum is on the mm scale, no more than approximately 100 of the 5000 cortical inputs on a given MSN are shared with any other MSN (Wickens and Arbuthnott, 2010). This organization confers exceptional input selectivity to MSNs on a combinatorial basis without the need for lateral inhibition, especially because numerous convergent excitatory inputs are required to overcome the strongly inhibitory K+ currents of MSNs for them to fire

(Wickens and Arbuthnott, 2010). The finely tuned selectivity of individual MSNs is suggested by electrophysiological findings that although MSNs responding to movement of a particular body part are located near each other (Alexander and DeLong, 1985b; Alexander and DeLong, 1985a), neighboring MSNs often have highly differing firing properties (Alexander and Crutcher, 1990; Crutcher and Alexander, 1990). Moreover, in paired recordings of MSNs, there is little correlation in action potential firing (Jaeger et al., 1995), even though subthreshold activity is tightly correlated (Stern *et al.*, 1997; Stern *et al.*, 1998).

While the organization of corticostriatal inputs allows MSNs to be extremely input selective, it also causes them to be broadly tuned. That is, any combination of the 5000 cortical inputs causing the MSN to reach threshold would generate an action potential. The broad tuning of MSNs to multiple patterns of cortical input could be sharpened through mechanisms of plasticity, which would strengthen the influence of certain inputs while diminishing others. In fact, extracellular recordings in awake animals during learning reveal changes in MSN responses to task-related stimuli acquired during learning (Kawagoe *et al.*, 1998; Shimo and Hikosaka, 2001; Lauwereyns *et al.*, 2002; Takikawa *et al.*, 2002). These acquired responses persist as long as performance is maintained (Aosaki et al., 1994).

Plastic changes in the striatum are tightly regulated by dopamine, which is poised to augment or curtail MSN responsiveness to a particular set of cortical inputs depending on their relationship to reinforcing behaviors. Dopamine synapses on spine necks of asymmetrical corticostriatal synapses (Freund et al., 1984; Groves et al., 1994) are the site of interaction for glutamate and dopamine release triggered by a reinforcing event

(Schultz *et al.*, 1993; Mirenowicz and Schultz, 1996)(see below). The conjunction of presynaptic and postsynaptic activity evoked in a slice preparation that would cause long term potentiation (LTP) in the cortex or hippocampus causes long term depression (LTD) in the striatum, which is depolarization dependent, requires activation of voltage sensitive Ca2+ channels, and necessitates an increase in intracellular Ca2+ concentration (Calabresi *et al.*, 1992b; Calabresi *et al.*, 1992c; Calabresi *et al.*, 1992d; Calabresi *et al.*, 1993; Lovinger *et al.*, 1993; Walsh and Dunia, 1993; Calabresi *et al.*, 1994; Kombian and Malenka, 1994). However, high frequency stimulation of glutamatergic inputs that normally evokes LTD in MSNs results in LTP when paired with pulsatile application of dopamine (Wickens et al., 1996). This LTP is blocked by D1 receptor antagonists (Kerr and Wickens, 2001), as is spike timing dependent potentiation (Pawlak and Kerr, 2008). Furthermore, D2 receptor antagonists have been shown to promote LTP in the corticostriatal pathway (Pawlak and Kerr, 2008).

The dynamics of dopamine signaling in plastic changes in the striatum observed using *in vitro* preparations are supported by findings from the intact animal. *In vivo* intracellular recordings demonstrate that high frequency stimulation of the cortex induces LTD in the corticostriatal pathway, but this same cortical stimulation induces short term potentiation when paired with 20 Hz stimulation of the SNr (Reynolds and Wickens, 2000). Furthermore, potentiation of hippocampal-evoked responses in the NAc following high frequency stimulation of the fimbria is blocked by the D1 receptor antagonist SCH23390 (Floresco et al., 2001). In the awake rat, intracranial self stimulation of SNr is behaviorally reinforcing, and results in the potentiation of corticostriatal synapses measured using *in vivo* intracellular recordings. What is more, the degree of potentiation

of corticostriatal synapses following ICSS-like stimulation of the SNr corresponded to the speed to reach ICSS criterion for individual rats (Reynolds et al., 2001). These points of evidence suggest that dopamine allows each MSN to develop specificity of responding to corticostriatal input following behavioral experience. Because of the architecture of inputs to the striatum, together with dopamine supported plasticity, combinatorial processing in MSNs allows for selective and specific signaling in the striatum.

B. ***Parallel and Integrative Processing in the Basal Ganglia***

Layered on top of combinatorial coding within striatal MSNs, the structure as a whole is roughly divided into functional domains that sustain individual aspects of learning and behavior. The topography of frontal cortical inputs to the striatum determines functional domains within the striatum, classically divided into sensorimotor, associative, and limbic regions (Parent and Hazrati, 1995; Masterman and Cummings, 1997; Cardinal *et al.*, 2002; Zgaljardic *et al.*, 2003; Robbins, 2007; Dalley *et al.*, 2008), listed from most dorsolateral to most ventromedial. Studies of human brain imaging have identified a functional-anatomical unity between areas of the cortex and striatum (Everitt and Robbins, 2005; Chudasama and Robbins, 2006; Remijnse *et al.*, 2006; Seger, 2008), demonstrating the importance of afferents to the striatum in determining patterns of activity. Frontal regions mediating reward, motivation, and affect regulation project mainly to the rostral striatum, especially the NAc, medial caudate, and medial and ventral putamen. Collectively, these striatal structures encompass the ventral striatum, which occupies more than 20% of the striatum in primates (Haber et al., 2006). As a consequence of the inputs it receives, the ventral striatum supports reward evaluation and

incentive based learning (Schultz *et al.*, 2000; Knutson *et al.*, 2001; Elliott *et al.*, 2003; Corlett *et al.*, 2004; Tanaka *et al.*, 2004).

The topography established in the striatum by the pattern of cortical innervation is conferred onto the pallidum and subsequently onto the thalamus, which targets specific areas of cortex depending upon its inputs. The mediodorsal and ventral lateral nuclei of the thalamus receive the bulk of pallidal and SNr efferents, as does the ventral anterior thalamic nucleus (Szabo, 1979; Haber *et al.*, 1990; Selemon and Goldman-Rakic, 1990; Hedreen and DeLong, 1991; Lynd-Balta and Haber, 1994; Middleton and Strick, 2002). Of these, the mediodorsal nucleus receives input from the medial SNr and ventral pallidum (Haber et al., 1985; Ilinsky et al., 1985), and targets the dorsolateral PFC, OFC, and anterior cingulate cortex (Giguere and Goldman-Rakic, 1988; Matelli and Luppino, 1996). The ventral anterior thalamus receives nigral inputs and projects to the rostral premotor and dorsolateral PFC, whereas the ventral lateral thalamus is innervated by motor regions of the dorsal pallidum, and targets motor and premotor areas of the frontal cortex. In this way, the functional domain topography is maintained from the cortex to the striatum, to the pallidum/nigra, to the thalamus, and back to the cortex (Middleton and Strick, 2000).

Information processing in these domains is not strictly segregated however. Basal ganglia circuits originating in cortex and subsequently influencing cortical activity represent parallel and integrative circuitry, in that functional domains are parsed, but there is also communication between these domains (Percheron and Filion, 1991; Bevan *et al.*, 1997; Redgrave *et al.*, 1999; Bar-Gad *et al.*, 2000; Haber *et al.*, 2000; Kolomiets *et al.*, 2001; McFarland and Haber, 2002; Haber, 2003; Haber *et al.*, 2006; Belin and

Everitt, 2008; Draganski *et al.*, 2008). The transfer of information across functional domains is supported by several features of basal ganglia circuit organization (Haber, 2003). Within the striatum, crosstalk along the "edges" of functionally distinct regions allows these border zones to process mixed signals. Furthermore, nodal points of convergence exist within corticostriatal and corticothalamic terminal fields, which can exist deep within individual domains. Communication between domains is facilitated by the anatomy of corticostriatal and pallidostriatal connections, which contain diffusely spread axonal arbors. Critically, many nonreciprocal arrangements between basal ganglia structures exist that are bidirectionally linked. Together, these aspects of basal ganglia processing support what has been described as an ascending spiral that allows motivation and cognition to influence motor planning (Haber, 2003), and are considered in more depth here.

The corticostriatal and striatopallidal projections are both characterized by several of the features that foster information transfer across domains. Cortical afferents to the striatum converge at the edges of functional domains, form nodal interfaces deep within functional domains, and establish diffuse projection systems from each cortical region extending through wide swaths of the striatum (Haber *et al.*, 2006; Calzavara *et al.*, 2007). There is also a high degree of convergence in the striatopallidal projection around the borders between functional domains. Moreover, individual pallidal neurons within dense focal striatal projection targets send dendrites into neighboring territories or target regions (Percheron and Filion, 1991). Connectivity between the striatum and pallidum further supports inter-domain communication in that the pallidum sends a reciprocal projection to the striatum, which innervates areas of the striatum from which the pallidal

source of the projection receives no input (Staines *et al.*, 1981; Beckstead, 1983; Haber *et al.*, 1985; Shu and Peterson, 1988; Kuo and Chang, 1992; Groenewegen *et al.*, 1993; Spooren *et al.*, 1996). This nonreciprocal bidirectional relationship with the striatum is particularly true of the GPe and ventral pallidum, and GPe forms reciprocal projections with the STN and lateral hypothalamus as well (Kuo and Carpenter, 1973; Kim *et al.*, 1976; DeVito and Anderson, 1982; Harnois and Filion, 1982). Finally, as recipient of basal ganglia output, the thalamus also contributes to information transfer between basal ganglia functional domains. The thalamus receives input from deep cortical layers, but innervates superficial (I/II), middle (III/IV), and deep (V) layers of the cortex after receiving input from the basal ganglia (McFarland and Haber, 2002; Erickson and Lewis, 2004), a pattern which mimics the nonreciprocal bidirectional projections present in the basal ganglia.

The organization of circuits connecting the striatum and midbrain dopamine neurons also enhances information transfer between different functional domains within the basal ganglia. The GPe and ventral pallidum afferent projection to the substantia nigra is marked by a high degree of overlap (Haber *et al.*, 1993; Bevan *et al.*, 1996), with convergence of multiple different inputs onto single dopamine neurons. Midbrain dopamine neurons are themselves divided into broad functional domains, in that the SNc provides inputs to more dorsal regions of the striatum dealing with cognition and motor control, whereas the ventral tegmental area (VTA) supports reward processes and reinforcement through its innervation of the ventral striatum. In rodents, the ventral striatum projects to the SNc, which projects to the dorsal striatum, thereby imbuing the limbic striatum with influence over the motor striatum (Nauta et al., 1978; Somogyi and

Smith, 1979). Similarly in primates, reciprocal and nonreciprocal connections between the striatum and midbrain dopamine neurons provide an anatomical substrate for the directional flow of information across multiple functional domains in the basal ganglia. Whereas the ventral striatum receives relatively little midbrain input, arising exclusively from the VTA, this striatal region projects to a large portion of the midbrain dopamine neurons, including the dorsal and ventral tiers of the VTA, SNc, and dorsal SNr. These midbrain areas provide massive input to the dorsal striatum, which itself influences a relatively small midbrain area (Haber et al., 2000). Taken together, the organization of glutamatergic and dopaminergic pathways within basal ganglia loops suggest that limbic and motivational information processed in ventromedial striatal domains is capable of shaping cognitive processing within the central striatum, and that information from both of these regions can influence motor control supported by the dorsolateral striatum.

C. *The Gating Hypothesis*

As a site of prefrontal cortical and limbic integration that can affect the activity of motor systems through basal ganglia loops, the ventral striatum is poised to convey limbic information to behavioral effectors. Individual MSNs in this region receive a convergence of inputs from multiple afferent structures; monosynaptic responses in NAc MSNs have been recorded intracellularly in the intact brain to mPFC, ventral hippocampus, basolateral amygdala, and the paraventricular nucleus of the thalamus (O'Donnell and Grace, 1995; Goto and O'Donnell, 2002), and extracellular recordings indicate convergence of multiple inputs onto individual MSNs as well (Finch, 1996). Furthermore, electron microscopic reconstruction of single MSNs combined with tract

tracing provide anatomical evidence for converging input from the mPFC, hippocampus, amygdala, and thalamus onto individual MSNs (French and Totterdell, 2002; French and Totterdell, 2003). These data suggest that individual MSNs serve as the site of limbic and prefrontal input integration.

In fact, relatively few NAc MSNs must be activated to support motivated behaviors; NAc processing occurs across a discrete, distributed ensemble of cells (Pennartz *et al.*, 1994; Lansink *et al.*, 2008; Nordquist *et al.*, 2008). These striatal ensembles are context specific, but overlap somewhat if the contexts are similar (Mattson et al., 2008). Moreover, learning within a particular context is blocked if the NAc ensemble specifically associated with that context is inactivated (Koya et al., 2009).

The gating hypothesis was originally proposed as a mechanism to explain how contextual information by way of the hippocampus may activate specific ensembles of MSNs in the NAc (O'Donnell and Grace, 1995; O'Donnell and Grace, 1998). This hypothesis, which posits that information flows through NAc MSNs only if the hippocampus first drives them into the up state, was formulated based upon observations from *in vivo* intracellular recordings. In the anesthetized rat brain, hippocampal stimulation evokes up states in NAc MSNs, and spontaneous up states in the ventral striatum require intact hippocampal inputs (O'Donnell and Grace, 1995). Single pulse stimulation of other inputs to the NAc, including the mPFC, only elicits action potentials from MSNs in the up state. What is more, LFP recordings in the hippocampus show a high degree of synchrony with NAc up and down states, whereas MSN up and down transitions do not appear to tightly synchronize with PFC LFPs in the anesthetized rat (Goto and O'Donnell, 2001b). Ventral striatal synchrony with the hippocampus bears out

in the behaving animal as well; single unit and field potential recordings have indicated that the NAc is entrained to the hippocampal theta rhythm with a high degree of coherence (Tabuchi *et al.*, 2000; Berke *et al.*, 2004). Furthermore, distributed subsets of neurons in the ventral striatum are active during spatial navigation tasks at decision points (van der Meer and Redish, 2009). These data suggest that the hippocampus selects the active ensemble of NAc MSNs appropriate for the behavioral context.

The hippocampus does not wield exclusive control over the activity of the NAc, however. MSNs in the ventral striatum can be driven by other inputs, including the basolateral amygdala (Goto and O'Donnell, 2002). Furthermore, an intact PFC is necessary for evoked NAc responses to ventral hippocampal stimulation in the anesthetized animal (Belujon and Grace, 2008), and PFC inactivation suppresses NAc activity in awake animals (Ishikawa et al., 2008). MSN responses to afferents summate sub- or supra-linearly depending on the order of afferent activation (Goto and O'Donnell, 2002; Carter *et al.*, 2007); PFC responses are potentiated following single pulse stimulation of hippocampal or amygdalar inputs, whereas PFC single pulse stimulation attenuates subsequent hippocampal responses (Goto and O'Donnell, 2002). These data suggest that the relationship between the PFC and NAc is more complex than would be expected for a monosynaptic excitatory connection.

The most significant challenge to the gating hypothesis is that it was based upon data generated using single pulse stimulation of the PFC. When activated in a behaving animal, however, the PFC fires in bursts (Chafee and Goldman-Rakic, 1998; Peters et al., 2005). Analysis of the relationship between PFC LFPs and NAc up states using a multi-taper sliding window approach revealed extremely high occasional coherence (Gruber et

al., 2009a), suggesting that the PFC can influence up state transitions in the NAc in certain instances. Furthermore, burst-like stimulation of the PFC reliably evokes up states in MSNs in the anesthetized rat (Gruber and O'Donnell, 2009). These up states notably lack action potential firing in most cases, and have been shown to include glutamatergic and GABAergic components in a slice preparation (Gruber et al., 2009b). This mix of excitatory and inhibitory influence over the PFC-evoked up state in NAc MSNs could reflect feed forward inhibition of MSNs following the PFC burst, as fast spiking interneurons are strongly activated by this stimulation (Gruber et al., 2009b). In the behaving animal, three way LFP recordings demonstrated that coherence between the hippocampus and NAc was strongest during spatial exploration, whereas PFC-NAc coherence was strongest during choice behavior in an operant task (Gruber et al., 2009a). Taken together, these data suggest that information processing in the ventral striatum is dynamic, and sensitive to continually updating environmental demands upon the animal or agent.

IV. *Function and Dysfunction in the Ventral Striatum: Motivated Behaviors and Psychiatric Disease*

A. *In Health*

The basal ganglia normally support voluntary movements as well as motivated behavior. Among the critical motivated behavioral functions supported by the basal ganglia are action selection (Mink, 1996; Redgrave *et al.*, 1999; Grillner *et al.*, 2005; Humphries *et al.*, 2006; Prescott *et al.*, 2006; Hikosaka, 2007) and reinforcement learning

(Schultz, 1998; Salamone and Correa, 2002; Wickens *et al.*, 2003; Wise, 2004; Houk, 2005; Schultz, 2006; Berridge, 2007).

Action selection is the process by which the brain resolves which functional system at any point in time should direct the "final common motor pathway," and in so doing determines behavioral output. The basal ganglia macroarchitecture is poised to handle the selection problem, as it contains parallel looped components originating from and returning to diverse cortically and subcortically based functional systems (Alexander et al., 1986; McHaffie et al., 2005), and is capable of integrative communication between these parallel loops. Because of this circuit organization, intrinsic processing in the basal ganglia can detect input saliencies depending on their comparative magnitudes in order to generate an output pattern allowing the disinhibition of the external structures providing the most salient input (Chevalier and Deniau, 1990; Gurney *et al.*, 2001b; Gurney *et al.*, 2001a; Humphries *et al.*, 2006).

Reinforcement learning is the process by which future action selection is biased to increase the probability of receiving reward or avoiding punishment. This process was initially described by Thorndike's Law of Effect in 1911, which asserts that "any act which in a given situation produces satisfaction becomes associated with that situation so that when the situation recurs the act is more likely than before to recur also." From a synaptic perspective, the basal ganglia enable reinforcement learning through two general mechanisms, namely presynaptic and postsynaptic changes in the striatum. First, the relative strengths of competing inputs are adjusted, such that when a stimulus is associated with reward, its representation in afferent structures to the basal ganglia is enhanced (Schultz, 2000; Kobayashi *et al.*, 2002; Watanabe *et al.*, 2002; Ikeda and

Hikosaka, 2003; Ding and Hikosaka, 2006; Kobayashi *et al.*, 2006). Second, the sensitivity of the striatum to receive these inputs can be changed, insomuch as responses to reinforced inputs are enhanced and responses to non-reinforced or punished inputs are diminished (Schultz, 1998; Reynolds and Wickens, 2002; Wickens *et al.*, 2003; Wise, 2004; Everitt and Robbins, 2005; Schultz, 2006; Arbuthnott and Wickens, 2007). These changes are largely conferred by phasic dopamine signaling reward prediction errors (Schultz, 1998).

Dopamine signaling in the striatum is critical for reinforcement learning. The unexpected presentation of reward or a neutral stimulus that predicts reward evokes phasic dopamine responses (Freeman *et al.*, 1985; Horvitz *et al.*, 1997; Schultz, 1998; Guarraci and Kapp, 1999), which are short latency (70-100 ms), short duration (100-200 ms) bursts of activity in midbrain dopamine neurons (Schultz, 1998). Whereas neutral sensory events initially elicit a phasic dopamine response, this response habituates rapidly if the stimulus is not associated with reward (Ljungberg et al., 1992), however the stimulus will evoke a phasic dopamine response again if it is later paired with reward (Ljungberg et al., 1992). Furthermore, if a primary reward is reliably predicted by a preceding stimulus, the primary reward will eventually cease to elicit a phasic dopamine response (Schultz, 1998; Pan *et al.*, 2005), and if the reward is predicted but fails to occur, a pause in dopamine cell firing occurs at the expected time of reward delivery (Schultz et al., 1997). Together, these data support the hypothesized role of dopamine neurons to signal reward prediction errors, that is, whether the outcome was better or worse than expected (Montague et al., 1996). Striatal neurons are poised to combine this dopamine reward prediction error with information about the action that elicited the

outcome (indeed, action-specific reward prediction error encoding neurons have been recorded in the dorsomedial striatum; (Stalnaker et al., 2012) in order to support learning.

Alternatively, the phasic dopamine signal may represent a sensory prediction error (Redgrave et al., 2008). Midbrain dopamine neurons receive much of their input from the superior colliculus, which can make preliminary estimates of biological salience (Boehnke and Munoz, 2008) and potential harm (Dean et al., 1989). Because of the nature of the afferent information they receive, midbrain dopamine neurons may be better suited for reinforcing assessments of agency (that is, whether an animal's actions produced a particular unexpected event) and for discovering novel actions (that led to the unexpected event) than reinforcing actions that maximize future reward (Redgrave and Gurney, 2006; Redgrave et al., 2008). This observation led to the agency hypothesis, which posits that the basal ganglia determine whether the agent is the likely cause of an unpredicted event, and then through dopamine-mediated plasticity, discover the causal components of behavioral output leading to that event (Redgrave and Gurney, 2006; Redgrave et al., 2008). In this model, the basal ganglia are able to determine agency because they receive glutamatergic signals from the cortex, thalamus, and limbic structures, which provide motor and sensory signals, in addition to a dopaminergic signal indicating a sensory prediction error. If the motor signal is missing, the unpredicted event likely occurred as a result of an external source. If it is present, however, the dopamine signal encourages the repetition of the preceding action (consider that dopaminergic pharmacological agents evoke stereotypic, repetitious behaviors; Redgrave *et al.*, 2010). Action repetition may result in repetition of the unpredicted event, which enables the determination of which behaviors reliably evoked the event.

Reinforcement learning describes not only the process of initially determining which behaviors lead to desired outcomes, but also the process by which these actions become habitual. Different compartments of the striatum have been found to support goal directed, action-outcome (A-O) behaviors, as well as habitual, stimulus-response (S-R) behaviors. The ventral and dorsomedial regions of the striatum are principally responsible for goal directed instrumental responding, in which the initiation of a response is controlled by the most current value of the outcome (Yin *et al.*, 2005b; Yin *et al.*, 2006). Habitual responding, by contrast, is supported by the activity of the dorsolateral striatum (Yin *et al.*, 2004; Yin and Knowlton, 2006), and involves the direct initiation of responding by a conditioned stimulus or context (Balleine and Dickinson, 1998). These two types of instrumental behaviors can be differentiated by the devaluation of the reinforcer (or goal; Belin and Everitt, 2010), in that goal directed behaviors are sensitive to devaluation, but habitual behaviors are not (Balleine *et al.*, 1995; Balleine and Dickinson, 1998; Yin *et al.*, 2004; Faure *et al.*, 2005; Yin *et al.*, 2005a; Yin *et al.*, 2006).

The hypothesis that the basal ganglia may mediate S-R learning was first proposed in the 1980s (Packard, 2010), and has since been supported by multiple behavioral studies. In rats, electrolytic (Packard et al., 1989) or excitotoxic (McDonald and White, 1993) lesions of the dorsal striatum disrupt approach behavior in an S-R modification of radial arm maze foraging, in which entry into light-cued arms is rewarded. The performance of lesioned rats is not disrupted, however, in the hippocampal dependent working-memory configuration of the task, which requires rats to visit only arms they have not previously entered for reward. Furthermore, S-R

performance in this task is insensitive to reinforcer devaluation produced by lithium chloride injection (Sage and Knowlton, 2000; Yin *et al.*, 2004; Yin *et al.*, 2005a). In a water maze task, dorsal striatal lesions do not disrupt spatial memory, evidenced by intact escape performance from the water onto a platform whose spatial location is fixed, however such lesions do interfere with habit learning, as evidenced by impaired escape when the platform location is varied, but always designated by the same visual cue (Packard and McGaugh, 1992; McDonald and White, 1994). The contribution of the dorsal striatum to habitual responding is also apparent in human studies. For instance, in a virtual reality town, dorsolateral striatum activation is associated with successful "route following," involving repeatedly following a fixed route, whereas hippocampal activation is associated with successful "way finding," involving the use of novel short routes (Hartley et al., 2003). Furthermore, temporal lobe amnesiacs can perform an S-R probabilistic classification task, but Parkinson's disease patients with dysfunction in the dorsal striatum cannot (Knowlton et al., 1996).

The transition of behaviors from goal directed to habitual is a naturally occurring process depending on dopamine sensitization, which develops after protracted instrumental training (Ahn and Phillips, 2007). The emergence of habitual control of behavior is facilitated by reinforcement schedules with weak contingency between responding and reward delivery, such as interval schedules (Hilario and Costa, 2008). In the plus maze, rats initially use a goal directed "place" strategy, in that they seek out a particular arm regardless of starting position, but following ongoing training switch to a habitual strategy, in which they always turn in a particular direction upon reaching the intersection of arms (Ritchie et al., 1950). This switch from an A-O to a S-R strategy is

accelerated by post-training intracranial injections of glutamate into the dorsolateral striatum (Packard, 1999). The well established contribution of dorsomedial and dorsolateral striatum to A-O and S-R driven behavior, respectively, is not mirrored by A-O or S-R specific activity in these regions, however (Stalnaker et al., 2010).

Pavlovian processes contribute critically to reinforcement learning in the striatum. Pavlovian conditioning encompasses behavioral and physiological changes that occur due to experiencing predictive relationships between neutral stimuli and appetitive or aversive events (Belin and Everitt, 2010). Multiple Pavlovian processes are encoded by striatal activity. Repeated pairing of neutral stimuli (conditioned stimuli, CS) with natural rewards (unconditioned stimuli, UCS) elicits conditioned approach to the CS (Brown and Jenkins, 1968). Activity in the central amygdala and NAc core underlie conditioned approach to food associated stimuli (Parkinson *et al.*, 1999; Parkinson *et al.*, 2000; Cardinal *et al.*, 2002; Parkinson *et al.*, 2002). This conditioned approach behavior can be quite strong; drug associated Pavlovian predictors elicit approach responses in the face of drug devaluation (Schoenbaum et al., 2004). The strength of Pavlovian cues over behavior is evident in that instrumental performance can be enhanced by non-contingently presented CSs, a phenomenon known as Pavlovian-to-Instrumental transfer. Instrumental behaviors on a weak reinforcement schedule are more sensitive to Pavlovian influence than those on a rich schedule (Lovibond, 1981; Holland and Gallagher, 2003), and as may be expected, Pavlovian responding has greater influence over S-R controlled instrumental behavior than A-O controlled behavior (Holland, 2004). Finally, CSs themselves may gain rewarding properties and act as conditioned reinforcers (Robinson

and Berridge, 1993), a feature of Pavlovian conditioning that may be especially relevant to drug addiction (see below).

Consistent with the recurring theme of parallel and integrative processing in the striatum, different domains of the striatum are implicated in distinct aspects of learning, however these modes of reinforcement learning exist on a continuum, which is reflected in the ascending integrative circuitry of the striatum. The ventromedial system, which includes the ventral striatum and its inputs from the amygdala, hippocampus, prefrontal cortex, and VTA, mediates the impact of Pavlovian stimuli on instrumental performance, including conditioned reinforcement and Pavlovian-to-Instrumental transfer (Cardinal *et al.*, 2002; Everitt and Robbins, 2005; Belin and Everitt, 2008), and interactions of the prefrontal cortex with the ventromedial striatum are critical for decision making (St Onge *et al.*, 2012). The dorsomedial system, which includes the dorsomedial striatum and its afferents from the prefrontal cortex, is involved in executive processes including goal-directed behavior, A-O learning, and modulation of instrumental incentive learning (Balleine, 2005). Finally, the dorsolateral system, including the dorsolateral striatum and its afferents from the sensorimotor and associative cortices as well as nigral sources of dopamine, supports habitual, S-R learning and behavior (Balleine, 2005). In this regard, the striatal processing of motivated behavior originates in the ventromedial striatum and spreads dorsolaterally with continued repetition.

B. *In Disease*

Dysfunction of basal ganglia circuits is characteristic of several neurological and neuropsychiatric disorders. The critical function of the basal ganglia in shaping

movement and motivated behavior is made obvious by the symptoms of disorders impacting this region, including Parkinson's Disease, Huntington's Disease, schizophrenia, and drug addiction. Special consideration is given to drug addiction as dysfunction in the ventral striatum and the corticostriatal projection are particularly implicated in this disorder.

1. *Parkinson's Disease*

Parkinson's Disease (PD) is a CNS degenerative disorder affecting midbrain dopamine neurons, which leads to impairments in motor function, skills, language, and cognition (Jankovic, 2008). The primary symptoms of PD are motor, including muscle rigidity, tremor, bradykinesia (slowing of movement), akinesia (loss of movement), and postural instability, due to reduced activation of the motor cortex by the basal ganglia in the absence of sufficient dopamine signaling in the striatum. The mechanism causing loss of dopamine neurons in PD is not fully understood, however a canonical feature of the disease is the accumulation of ubiquitinated complexes of α-synuclein called Lewy bodies prior to DA cell death (Gai *et al.*, 2000; McNaught and Jenner, 2001).

Treatment strategies for PD have provided a serendipitous opportunity to gain insight into circuit level changes in human patients with the disease. Although the first line treatment for PD is l-DOPA dopamine replacement therapy, more advanced PD is better controlled with deep brain stimulation (DBS) of basal ganglia nuclei such as STN and GPi (Benabid *et al.*, 2006). The implanted stimulating electrodes can then be used to record aberrant electrical activity in these nuclei prior to their use for delivery of high frequency stimulation. DBS macroelectrode recordings in individuals suffering from PD

have unveiled abnormal oscillatory activity in STN and GPi. These include low frequency, tremor related oscillations at 4-8 Hz, as well as unusual oscillations in the α (8-13 Hz), β (15-30 Hz), and γ (30-100 Hz) bands (Foffani *et al.*, 2003; Chen *et al.*, 2007; Hammond *et al.*, 2007; Weinberger *et al.*, 2009). Interestingly, a reduction in the amplitude of these abnormal oscillations following pharmacological intervention is well correlated with reduced tremor scores and clinical improvement (Amirnovin et al., 2004; Hammond et al., 2007).

2. *Huntington's Disease*

Like PD, Huntington's Disease (HD) is known primarily as a disease of motor function, but gravely affects cognition and mood as well. HD is a genetic, progressive, autosomal dominant neurological disorder. Its symptoms include abnormal, uncontrolled movements (chorea), cognitive disturbances, and disorders of mood (Harper, 1996), all of which are disruptions of functions supported by basal ganglia activity. The HD gene (ITI5) is located on the short arm of chromosome 4, and disorder in this gene leads to a CAG (glutamine) expansion, usually exceeding 40 repeats in length in the disease state (Group, 1993). This gene normally encodes a cytoplasmic protein (huntingtin protein) that is associated with membranes and microtubules, implying its probable role in trafficking, exocytosis, or endoyctosis (DiFiglia et al., 1995). HD is characterized by neuronal loss in the striatum and cortex (DiFiglia et al., 1995), with particular loss of MSNs in the striatum (Vonsattel et al., 1985). Neuronal dysfunction precedes cell degeneration and death, and is likely a major cause of symptoms (Levine et al., 2004). D2 MSNs are more sensitive to the deleterious effects of HD, and are lost before D1

MSNs. Because D2 indirect pathway MSNs receive a stronger cortical input (from PT cortical neurons, see above), their enhanced vulnerability to cell death in HD has led to the hypothesis that cortical signals become overwhelming and unregulated in HD, resulting in compensatory corticostriatal disconnection and apoptosis (Papadia and Hardingham, 2007). For this reason, the corticostriatal pathway may represent a prime target for the treatment of HD (Li et al., 2003).

3. *Schizophrenia*

Schizophrenia is a complex psychiatric disorder characterized by multiple diverse symptoms. These symptoms are typically divided into positive, negative, and cognitive groups, which represent aberrant behaviors or experiences present in the disease state not present in healthy individuals, normal drives or behaviors missing in the disordered individual, and disruption to normal cognition, respectively (DSM IV, APA, 2000). For instance, traits of psychosis such as hallucinations or delusions are considered positive symptoms, whereas avolition and social withdrawal are considered negative symptoms, and disrupted working memory is considered a cognitive symptom of schizophrenia. Early hypotheses of the neural dysfunction underlying schizophrenia focused largely on excess dopamine signaling, due primarily to the efficacy of dopamine antagonists in treating positive symptoms (Carlsson and Lindqvist, 1963; Seeman, 1987). More recent investigation, however, has suggested that schizophrenia arises from a pervasive imbalance of excitatory and inhibitory signaling in the brain which implicates multiple brain regions, cell types, and transmitter systems in the disorder (O'Donnell, 2011). Abnormalities in the PFC in particular have been repeatedly demonstrated in individuals

suffering from schizophrenia (Harvey *et al.*, 1993; Andreasen *et al.*, 1994; Buckley *et al.*, 1994; Selemon *et al.*, 1995; Yurgelun-Todd *et al.*, 1996), as has disruption to the hippocampus and temporal lobes, the amygdala, and the thalamus (see (O'Donnell and Grace, 1998) for review).

As a target of multiple regions affected in schizophrenia, and a major hub of dopamine signaling in the brain, the NAc is uniquely vulnerable to dysfunction in schizophrenia. In fact, abnormality of the NAc has been reported in individuals suffering from schizophrenia; the volume of this structure is reduced in postmortem brains from people with the disorder (Pakkenberg, 1990; Pakkenberg, 1993). Moreover, disruption of hippocampal gating of cortical signals in the NAc has been proposed to underlie all three symptom clusters in schizophrenia (O'Donnell and Grace, 1998). More recently, prefrontal cortical interneuron dysfunction yielding a disinhibited PFC has been suggested to underlie the symptoms of schizophrenia (Beasley and Reynolds, 1997; Lewis et al., 2005; O'Donnell, 2012). Such an overactive cortex could lead to abnormal NAc activation, which is in fact observed in individuals suffering from schizophrenia (Liddle *et al.*, 1992; Busatto *et al.*, 1995). Therefore, although cortical deficits may be a primary aspect of schizophrenia pathophysiology, integration of information in ventral striatal circuits may play a critical role in several symptom domains.

4. *Addiction*

Protracted exposure to drugs of abuse, particularly psychostimulants which are considered in particular here, misappropriates processing in basal ganglia circuitry, leading to drug addiction. Drug addiction is a brain disease (Leshner, 1997), described

by the DSM IV as a chronic relapsing disorder characterized by loss of control over drug intake and compulsive drug use that persists despite adverse consequences (DSM IV, APA, 2000). This highly complex disorder consists of a multifactoral pathology that results in compounded reinforcement of not only the direct effects of the drugs themselves, but also of the cues that are associated with them. Because psychostimulants directly activate the brain's mechanisms of positive reinforcement, they enhance the incentive values of environmental cues repeatedly paired with drugs through a process called incentive sensitization (Robinson and Berridge, 1993; Robinson and Berridge, 2000; Robinson and Berridge, 2001; Robinson and Berridge, 2003). Moreover, psychostimulants accelerate habitual responding, such that drug use is rapidly controlled by environmental cues rather than the hedonic value of the drug (Everitt and Robbins, 2005). Psychostimulants also impair prefrontal cortical functions like behavioral control (Bornovalova et al., 2005; Verdejo-Garcia et al., 2007) and planning (Bechara et al., 2001; Bolla et al., 2003; Franken et al., 2007). Finally, withdrawal triggers progressively worsening negative affective states, a phenomenon known as hedonic allostasis, which encourages compulsive drug use (Koob and Le Moal, 2001; Koob and Le Moal, 2005; Koob and Le Moal, 2008).

Psychostimulants use the dopamine dependent striato-nigro-striatal ascending spirals linking the NAc to the dorsal striatum to rapidly induce a shift from A-O to S-R mechanisms in the control of drug seeking (Everitt and Robbins, 2005; Belin and Everitt, 2008). Psychostimulants mimic the dopamine increases associated with phasic dopamine neuron firing that codes salience and reward (Schultz, 2000) by blocking reuptake (cocaine blocks the dopamine transporter) or increasing release (amphetamines bind the

vesicular monoamine transporter to promote the release of monoamines). These actions cause dopamine increase in multiple brain regions targeted by midbrain dopamine neurons, including the dorsal and ventral striatum, the pallidum, the STN, the amygdala, and the PFC (Brown *et al.*, 1979; Meibach and Katzman, 1979; Campbell *et al.*, 1985; Lavoie *et al.*, 1989). With repeated administration of psychostimulants, sensitization occurs, that is, the same dose of psychostimulant induces progressively enhanced DA release (Robinson and Becker, 1982; Robinson *et al.*, 1982; Robinson *et al.*, 1988; Pierce and Kalivas, 1997; Belin *et al.*, 2007). A common action of all drugs of abuse is to increase dopamine transmission within the NAc (Di Chiara and Imperato, 1988), a commonality indicating that the mesolimbic pathway projecting from the VTA to the NAc and olfactory tubercle mediates the reinforcing effects of addictive drugs (Ikemoto, 2007).

Reduced dopamine binding in the NAc is associated with addiction, and may both result from and predispose for compulsive drug taking. Withdrawal from extended access cocaine results in a reduction of dopamine in the NAc (Weiss et al., 1992), leading to dysphoria and a lack of interest in natural rewards. Furthermore, low levels of D2 receptor binding in the striatum have been observed in cocaine addicts (Volkow et al., 1993). Reduced D2 receptor expression may be a pre-existing condition increasing the vulnerability to addiction in some individuals, however. In drug naïve monkeys, low D2 receptor binding in the NAc predicts subsequent cocaine self-administration (Nader et al., 2008), and low D2/3 ligand binding in rat NAc predicts escalation of cocaine self administration (Dalley et al., 2007). Together with sensitized dopamine release upon repeated drug administration, this reduced D2 receptor expression may render

psychostimulants optimally reinforcing and maintain drug seeking (Goldstein and Volkow, 2002).

Multiple basal ganglia structures and their afferents contribute to addiction. The acquisition of cue-controlled cocaine seeking depends on the basolateral amygdala (Whitelaw et al., 1996) and the NAc core (Di Ciano and Everitt, 2001; Ito et al., 2004), as well as the interaction between these structures (Di Ciano and Everitt, 2004b). The OFC (Hutcheson and Everitt, 2003; Everitt *et al.*, 2007) and the VTA (Di Ciano and Everitt, 2004a) are also necessary structures in the acquisition of cue-induced drug seeking. Well established cue-evoked cocaine seeking, however, depends upon dopamine action in the dorsolateral striatum (Ito et al., 2002). The transfer of drug seeking and taking from a goal directed to a habitual process occurs rapidly, such that the dorsolateral striatum plays an important role in addiction behavior. The emergence of habitual, dorsolateral striatum governed behavior is accelerated following cocaine or alcohol exposure (Dickinson et al., 2002; Miles et al., 2003). Moreover, dorsolateral striatum activation is associated with craving elicited by the presentation of drug associated cues in addicted individuals (Garavan et al., 2000; Volkow et al., 2006; Wong et al., 2006). In rats, dorsolateral striatum inactivation blocks relapse to drug seeking after abstinence (Fuchs et al., 2006; See et al., 2007).

It has been proposed that the shift of cue-induced drug seeking from the NAc to the dorsolateral striatum underlies the development of habitual drug seeking (Everitt and Robbins, 2005; Takahashi et al., 2007). This transition is executed through the dopamine dependent connectivity linking the NAc to the dorsolateral striatum (Haber et al., 2000) described above), which links incentive motivation to cognitive processes (Everitt and

Wolf, 2002; Everitt and Robbins, 2005; Yin and Knowlton, 2006; Everitt *et al.*, 2008; Haber, 2008; Belin *et al.*, 2009). In fact, disconnection between the NAc and dopaminergic control over the dorsolateral striatum impairs cue-induced cocaine seeking to the same degree as dopamine receptor blockade in the dorsolateral striatum (Belin and Everitt, 2008).

The transition of goal directed behaviors to incentive driven habits in and of itself is not detrimental. However, the rapid establishment of drug seeking as a habitual response to drug associated cues may become pathological when prefrontal executive control over these incentive habits is lost (Jentsch and Taylor, 1999; Robbins and Everitt, 1999; Everitt and Robbins, 2005; Kalivas and Volkow, 2005). In the normal human brain, the PFC exerts inhibitory influence over the NAc and VTA when behaviors resulting in immediate reward must be suppressed in favor of long-term goal achievement (Diekhof and Gruber, 2010). Repeated exposure to drugs of abuse alters synaptic responses and plasticity in the corticostriatal pathway (Luscher and Malenka, 2011) and impairs the performance of PFC-dependent tasks such as visual attention, delay discounting, reversal learning, and decision making, and is associated with increased impulsivity. Disrupted behavior on these tasks has been observed in drug addicted humans (Moeller *et al.*, 2002; Hester and Garavan, 2004; Kirby and Petry, 2004) and drug exposed animals (Paine *et al.*, 2003; Paine and Olmstead, 2004; Schoenbaum *et al.*, 2004; Dalley *et al.*, 2005a; Dalley *et al.*, 2005b; Black *et al.*, 2006; Calu *et al.*, 2007; George *et al.*, 2008). This reduced top-down cortical control may even facilitate Pavlovian influences on instrumental drug seeking (Schoenbaum *et al.*, 2004;

Schoenbaum and Setlow, 2005; Schoenbaum *et al.*, 2006; Schoenbaum and Shaham, 2008).

5. *Dysfunction in the Basal Ganglia: A Summary*

The gravity of dysfunction in the basal ganglia and ventral striatum is underscored by the severity of disorders arising from it. In order to identify the alterations in striatal information processing contributing to disease and disorder, it is critical first to understand normal modes of striatal function. The Gating Hypothesis posits that contextual information by way of the hippocampus selects the ensembles of NAc MSNs capable of transmitting cortical information onward to the pallidum, however this model fails to account for the effects of strong PFC activation on NAc information processing. Here, I consider the complex relationship of PFC with the ventral striatum, and investigate what impact that relationship has on information processing in the NAc.

V. *Hypotheses and Predictions: Closing the Gate in the Limbic Striatum*

The complexity of elements contributing to information processing within the ventral striatum is evident in the data reviewed above. As useful as the Gating Hypothesis has been to explain some behavioral aspects of ventral striatal function, it falls short of a thorough explanation of the role of dynamic patterns of cortical activity on information processing in this region. Although the additive nonlinear interaction that characterizes the gating hypothesis has been proposed to underlie the use of contextual information to guide motor plans, it may not be adequate to explain interactions during goal-directed behaviors and in decision-making instances. In those instances, interactions among inputs to the VS may assume a different profile. PFC neurons fire in bursts during instrumental behavior (Chafee and Goldman-Rakic, 1998; Peters et al., 2005), and robust, burst-like activation of the PFC reliably produces up states in VS MSNs (Gruber and O'Donnell, 2009). Furthermore, during behavioral epochs marked by burst firing in the PFC, the synchrony typically observed between the VS and the HP as coherent theta oscillations is lost in favor of a period of VS entrainment to the PFC (Gruber et al., 2009a). These findings suggest that the PFC is capable of disengaging the VS from the HP; thus, one excitatory projection may somewhat paradoxically reduce the efficacy of another glutamatergic input in VS MSNs.

A requirement for that possibility is that strong PFC activation will attenuate the impact of hippocampal afferents onto VS MSNs. Although input integration is typically additive for excitatory projections, competition among converging inputs can also occur. For example, in hippocampal slices, one set of inputs to CA1 neurons may reduce the efficacy of another (Lynch *et al.*, 1977; Alger *et al.*, 1978), and in the PFC, similar

interactions between cortical and thalamic inputs have been reported (Fuentealba et al., 2004).

The main hypothesis tested here is that high frequency bursting in the PFC transiently suppresses VS responses to glutamatergic inputs through feed-forward inhibition of MSNs. I further hypothesized that such a relationship with MSNs is specific to the PFC and not characteristic of other glutamatergic afferents to the VS, as the generation of silent up states in VS MSNs following PFC train stimulation was a novel finding not reflecting known MSN responses to train stimulation of other afferents. Moreover, the striatal PV interneurons enabling feed forward inhibition over MSNs are densely innervated by cortical afferents, with fewer inputs arriving from other regions such as the thalamus. Several predictions arise from these hypotheses. I predicted that burst-like stimulation of the PFC would reduce the magnitude of EPSPs arising from HP stimulation at a short latency following the PFC train, but that the HP response would recover at longer latencies after PFC train stimulation. I reasoned that shunting of synaptic responses through feed-forward inhibition should not exclusively impact HP responses, so I predicted that burst-like stimulation of the PFC would reduce the magnitude of EPSPs arising from thalamic stimulation. In line with my second hypothesis, I predicted that high frequency stimulation of HP or thalamic afferents to the VS would not suppress PFC-evoked EPSPs. Finally, as my hypothesized mechanism for a PFC-evoked suppression of synaptic responses in VS MSNs necessitates an inhibitory mediator, I predicted that antagonism of $GABA_A$ signaling in the recorded MSN would reduced the magnitude of PFC-driven heterosynaptic suppression.

Materials and Methods

I. *Animal subjects*

Intracellular recordings from MSNs were obtained *in vivo* from 51 adult male Long Evans rats (310 – 460 g) purchased from Charles River Laboratories (Wilmington, MA). All experiments were conducted in accordance with the United States National Research Council *Guide for the Care and Use of Laboratory Animals* and were approved by the University of Maryland Institutional Animal Care and Use Committee.

II. *Electrophysiological Recordings*

In preparation for recording, rats were deeply anesthetized with chloral hydrate (400 mg/kg, i.p.), and placed in a stereotaxic apparatus (David Kopf, Tujunga, CA). Anesthesia was maintained throughout the duration of experiments by constant i.p. infusion of chloral hydrate (20-30 mg/kg/hr) via a minipump (Bioanalytical Systems, West Lafayette, IN). Throughout recording experiments, rats were kept between 36º and 38º C as measured by a rectal temperature probe (Fine Science Tools, Foster City, CA). Bupivacaine (0.25%) was injected subcutaneously into the skin overlying the skull before a scalpel incision was made. Small burr holes were drilled into the skull to allow for electrode placement. A bipolar concentric stimulating electrode (outer diameter, 1 mm) with 0.5 mm of separation between the tips (Rhodes Medical Instruments, Woodland Hills, CA) was placed into the right medial PFC (3.2 mm anterior to bregma, 2.0 mm lateral to midline, 4.4 mm ventral to the pial surface) at a 30º angle toward midline. As a result of this protocol, the electrode entered the brain from the left of the midline and crossed into the right hemisphere with the tip terminating in the infralimbic/prelimbic region of the medial PFC. A second stimulating electrode was placed into the right

fimbria (2.8 mm posterior to bregma, 3.8 mm lateral to midline, 4.2 mm ventral to the pial surface). In a subset of animals (n = 14), the second stimulating electrode was placed into the right thalamus (2.8 mm posterior to bregma, 3.0 mm lateral to midline, 4.2 mm ventral to the pial surface) instead of the fimbria. Current pulses through the stimulating electrodes were generated by Isoflex stimulus isolation units (AMPI, Jerusalem, Israel) driven by a Master 8 Stimulator (AMPI).

Intracellular microelectrodes were pulled from borosilicate glass tubing (1 mm outer diameter; World Precision Instruments, Sarasota, FL) to a resistance of 40-110 MΩ using a P-97 Flaming-Brown microelectrode puller (Sutter Instruments, Novato, CA). Recording electrodes were filled with 2% Neurobiotin (Vector Laboratories, Burlingame, CA) in 2 M potassium acetate and lowered into the right limbic striatum (1.2 – 1.8 mm anterior to bregma, 1.2 – 1.4 mm lateral to midline, 3.5 – 6.5 mm below the pial surface) using a 2662 direct drive micropositioner (David Kopf). In 15 animals, 200 μM picrotoxin (Sigma-Aldrich, St. Louis, MO), the $GABA_A$ open channel blocker, was included in the intracellular solution contained in the recording electrode. Electrical signals from impaled cell membranes passed through a chloride coated silver wire housed inside the glass microelectrode via a headstage to an intracellular amplifier (IR-283, NeuroData, Delaware Water Gap, PA). Intracellular signals were lowpass filtered at 2 kHz (FLA-01, Cygnus Tech. Inc., Delaware Water Gap, PA), digitized (Digidata 1322A, Axon Instruments, Union City, CA), sampled at 10 kHz using Axoscope (Axon Instruments), and stored on a PC.

III. *Stimulation Protocol*

Once impaled, neurons were recorded in current clamp mode at baseline for at least five minutes to ensure stability of membrane properties. Only cells exhibiting a resting membrane potential of at least -65 mV and action potential amplitude of at least 40 mV from threshold were used in this study. A series of positive and negative current steps delivered through the recording electrode (0.1 – 0.5 nA, 100 ms) were used to assess the input resistance of recorded cells. Subsequent to baseline recordings, the responses of stable cells to medial PFC and fimbria stimulation were assessed using the following protocol once every 15 seconds for 8 – 15 repetitions. A single-pulse stimulation of the fimbria (1.0 mA; 0.5 ms; F1) was delivered 500 ms before train stimulation of the mPFC (50 Hz train of 10 pulses; 0.4 – 1.0 mA; 0.5 ms). A second fimbria pulse (1.0 mA; 0.5 ms; F2) was then delivered either 50 ms or 500 ms after the last pulse in the train stimulation of the PFC. This protocol was intended to test the effect of burst-like PFC stimulation on MSN responses to hippocampal inputs in the limbic striatum. An equivalent protocol (single pulse stimulus to the thalamus, followed by a 10 pulse, 50 Hz train stimulation of the PFC at a 500 ms latency, followed by a second pulse to the thalamus at a 50 or 500 ms latency) was used in the animals receiving thalamic stimulating electrode placement. The response of cells to fimbria or thalamus single pulse stimulation 50 ms following single pulse stimulation of the PFC was also considered in a subgroup of cells (n = 13). In some cases (n = 12), I injected depolarizing current through the recording electrode (between -0.2 nA and 0.2 nA) to record an F1 or T1 response during a depolarized membrane potential similar to that at which F2 and T2 responses were evoked. A subset of cells (n = 13) was also subjected to a stimulus protocol in

which a single pulse stimulus was delivered to the PFC (1.0 mA; 0.5 ms; PFC1), followed at a 500 ms latency by a train stimulation of the fimbria or thalamus (50 Hz train of 10 pulses; 1.0 mA; 0.5 ms), after which a second pulse was delivered to the PFC (1.0 mA; 0.5 ms; PFC2). In all cases, responses to stimulation were averaged over all of the repetitions delivered to the cell.

IV. ***Magnitude of Suppression Calculation***

To calculate the magnitude of EPSP suppression, I first determined the ratio of the control and test pulses. For instance, in the cases in which I stimulated the fimbria, I calculated F2/F1 using response amplitudes. As this quotient represents the proportion of the response retained following PFC train stimulation, I expressed the difference between 1 and F2/F1 as a percentage to indicate the magnitude of EPSP suppression.

V. ***Histology***

After baseline and stimulus-response recordings were collected, cells were filled with Neurobiotin by passing positive current (1 nA, 200 ms pulses, 2 Hz) for at least 10 min through the recording electrode. Upon completion of recording experiments, animals were euthanized with an overdose of sodium pentobarbital (100 mg/kg) and transcardially perfused with cold saline followed by 4% paraformaldehyde. Brains were then removed and postfixed in 4% paraformaldehyde for at least 24 hrs before being transferred to a 30% sucrose solution in 0.1 M phosphate buffer. After at least 48 hrs in sucrose, brains were cut into 50 µm sections using a freezing microtome and placed into phosphate buffer. Sections through PFC and fimbria or thalamus were mounted on gelatin-coated slides and Nissl stained to verify placement of stimulating electrodes. Sections through VS were processed for visualization of Neurobiotin-filled cells, and

then mounted on gelatin-coated slides and Nissl stained. All stained slides were coverslipped and examined microscopically for cell and electrode location.

Results

I performed *in vivo* intracellular recordings in 69 neurons from 51 adult male rats. A subset of these cells (n = 10) were processed for Neurobiotin labeling and were morphologically identified as MSNs (Figure 2A). All neurons included in this study were located within the striatal region receiving afferents from the medial PFC and HP (Voorn et al., 2004), including the nucleus accumbens core and the ventral aspect of the dorsomedial striatum (Figure 2B). All recorded cells exhibited spontaneous transitions between negative resting membrane potentials (down states; -84.1 ± 8.1 mV, mean ± SD) and depolarized up states (-70.9 ± 7.2 mV) closer to action potential threshold (Figure 2C). Up states occurred at a frequency of 0.6 ± 0.2 Hz with a duration of 521.8 ± 180.8 ms. The majority of recorded neurons were silent (n = 29/47; 62%), but spontaneous firing was detected in the remaining 18 neurons at 0.96 ± 1.4 Hz (range, 0.01 – 5.2 Hz). Action potentials (spontaneous or evoked) in all neurons had an amplitude of 52.8 ± 7.9 mV from threshold. Input resistance in the down state was 54.5 ± 17.4 MΩ. These properties are similar to what has been previously reported in VS MSNs (O'Donnell and Grace, 1995; Goto and O'Donnell, 2001b; Goto and O'Donnell, 2001a; Brady and O'Donnell, 2004).

I. *High Frequency PFC Stimulation Suppresses Fimbria-evoked Synaptic Responses in MSNs*

To assess whether robust PFC activation suppresses MSN responses to HP afferents, stimulating electrodes were targeted to the medial PFC and the fimbria-fornix, the fiber bundle carrying HP inputs to the VS (n = 21 neurons; Figure 2D). Single-pulse fimbria stimulation evoked excitatory postsynaptic potentials (EPSPs) with a mean

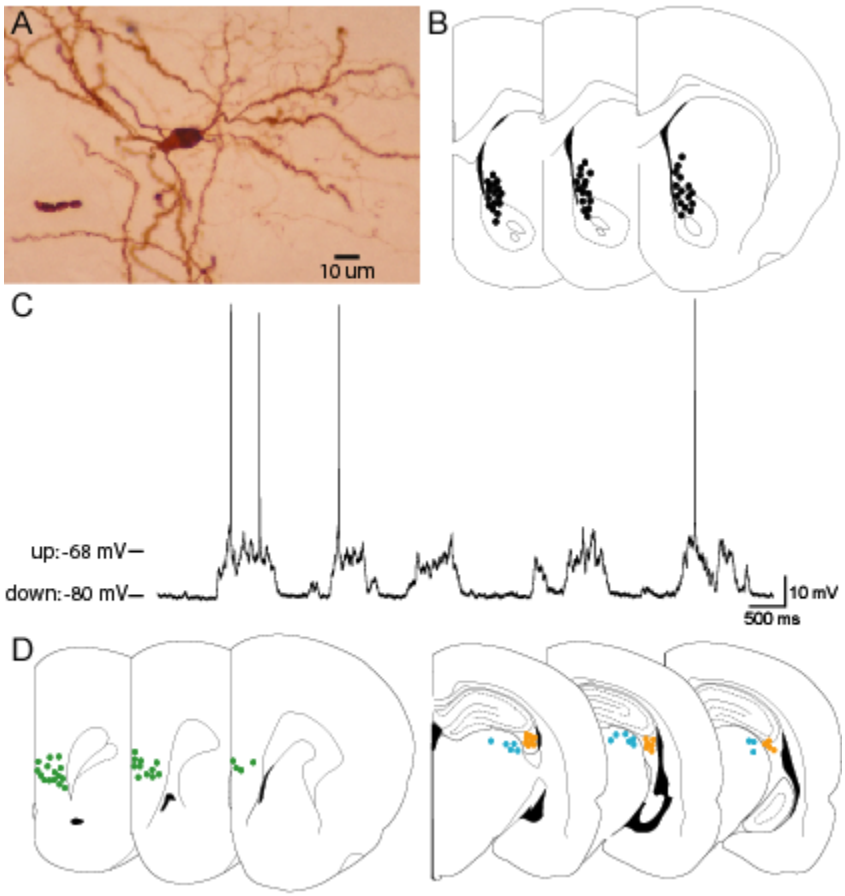

Figure 2. Intracellular recordings of Medium Spiny Neurons *in vivo*
(A) Image of an MSN filled with Neurobiotin and visualized with a DAB reaction.
(B) Illustration of recording sites in the VS (dots represent cell locations). Recorded cells fell within the nucleus accumbens core, as well as dorsal to the classical nucleus accumbens boundaries, but within the region receiving afferents from the PFC and HP (Voorn, 2004).
(C) Representative trace showing spontaneous membrane potential of an MSN with transitions between a resting (down) state and the more depolarized up state at a frequency of 0.7 Hz. Action potentials originate exclusively from the up state.
(D) Illustration showing the location of stimulating electrode tips in the medial PFC (left, green, including both prelimbic and infralimbic regions), fimbria (right, orange), and dorsolateral thalamus (right, blue).

amplitude of 7.6 ± 5.3 mV and time to peak of 36.1 ± 16.3 ms. Consistent with previous results (Gruber and O'Donnell, 2009), 10 pulse, 50 Hz train stimulation of the PFC elicited a prolonged depolarization, but rarely action potentials in VS MSNs (Figure 3A). Only four of 27 MSNs responded with action potential firing during the PFC train stimulation; the majority remained silent during the PFC-evoked depolarization. I evaluated MSN responses to fimbria stimulation before and following PFC burst stimulation. At a short, 50 ms latency following the final pulse in the PFC train stimulus, the amplitude of the fimbria-evoked EPSP (F2) was 1.7 ± 2.0 mV, a value significantly reduced compared to the fimbria-evoked EPSP recorded 500 ms prior to PFC stimulation (F1) ($t_{(13)} = 5.679$; $p < 0.0001$; Figure 3A), without affecting time to peak. Not only was this suppression apparent in the group comparison, but it was also evident for each individual cell. I measured the amplitude of the F1 and F2 responses in each repetition of the stimulus protocol, such that I was able to compare these values with a paired t test for each cell. In all of the MSNs tested, the F2 response was significantly attenuated 50 ms following the PFC train ($p < 0.01$ in 12/14 cells; $p < 0.05$ in the remaining 2/14 cells). HP afferent stimulation 500 ms after the last pulse in the PFC train did not show a suppression relative to the F1 response ($t_{(11)} = 1.462$; $p = 0.17$; Figure 3B). Only three of the twelve MSNs tested showed a significant suppression of the F2 response 500 ms following the PFC train. These data indicate that strong PFC activation similar to what is observed during instrumental behavior in awake animals transiently attenuates synaptic responses to HP afferents in VS MSNs.

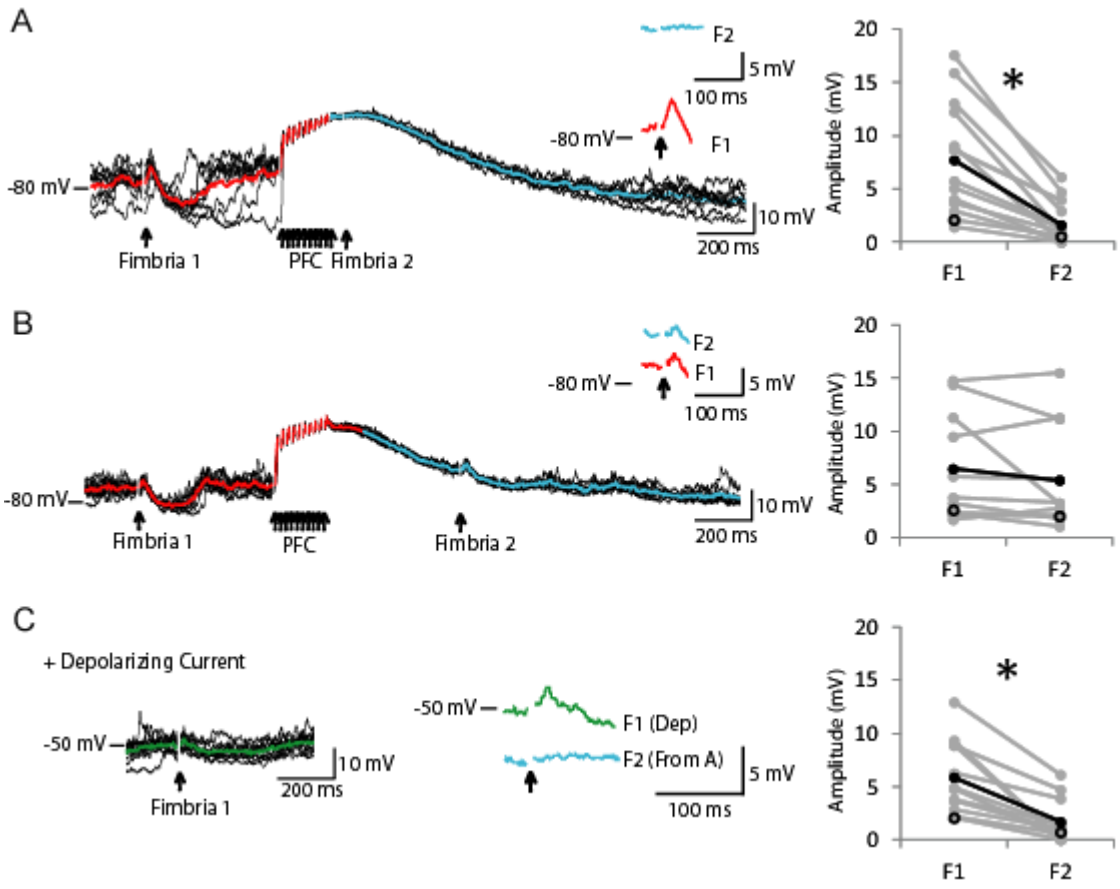

Figure 3. PFC high frequency stimulation inhibits fimbria-evoked EPSPs in MSNs at short, but not long latencies

(A) Multiple overlaid sweeps showing a VS neuron's response to combined stimulation of PFC and HP inputs. An initial control pulse to the fimbria (F1) was followed by a train of 10 pulses (50 Hz) to the PFC, and a test pulse to the fimbria (F2) 50 ms following the PFC train. Mean responses to F1 and F2 are highlighted in red and blue, respectively, and the initial 100 ms of both responses are shown as an inset. Right: Actual amplitude values of all F1 and F2 evoked responses are shown in gray (example traces indicated in open black circles in this and subsequent figures), while average values are shown in closed black, revealing a significant attenuation of F2 (* $p < 0.0001$; paired t test).

(B) Similar display illustrating responses obtained when F2 was delivered 500 ms following the PFC train stimulus. Mean responses to F1 and F2 are again shown as an inset, and plots to the right illustrate all F1 and F2 values obtained from this protocol, which did not significantly differ.

(C) Overlay of traces and their average (green) recorded using a similar protocol (traces clipped prior to delivery of the PFC train), but with F1 evoked at a depolarized membrane potential. Injection of depolarizing current into the cell did not significantly reduce the amplitude of the response to the control fimbria stimulus. In the inset, the mean response of the cell to the F1 stimulus during current injection is highlighted in green and compared to its mean response to the F2 stimulus (shown in *A*). Right: Actual amplitude values of all depolarized F1 and basal F2 responses (gray) and their average (black), revealing an attenuation of F2. (* $p < 0.0003$; 2 tailed paired T test).

Because PFC train stimulation evoked a sustained depolarization in MSNs, it is possible that the attenuation observed in F2 EPSPs resulted from the depolarization itself; the membrane potential may have neared the reversal potential of the fimbria-evoked response following the PFC stimulation. To evaluate this possibility, I assessed F1 and F2 EPSP magnitudes evoked at similar membrane potentials. I achieved these conditions either by considering F1 EPSPs evoked during spontaneous up states (8 neurons) or by injecting depolarizing current into the recorded cells through the recording electrode (4 neurons). I tailored the amount of current injected individually for each cell to adjust the membrane potential to that achieved by the PFC train. When I compared F1 and F2 EPSPs recorded at similar membrane potentials, the amplitude of the F2 EPSP evoked 50 ms after the PFC train was still attenuated relative to that of the depolarized F1 EPSP ($t_{(11)} = 5.304$; $p < 0.0003$; Figure 3C). These data suggest that depolarization-induced changes in ionic conductances are not responsible for the PFC-evoked attenuation of the F2 EPSP.

Stimulating HP afferents twice within a few hundred milliseconds could suppress the second response independently of any effect of the intervening PFC stimulation. To address this possibility, I omitted the PFC train from the stimulus protocol in a subset of neurons (n = 6). In these cases, I found no difference in EPSP amplitude between the F1- and F2-evoked responses ($t_{(5)} = 0.506$; $p = 0.635$; Figure 4A). Furthermore, a single-pulse PFC stimulus did not reduce the amplitude of the F2 EPSP evoked 50 ms after the PFC pulse ($t_{(5)} = 0.266$; $p = 0.80$; Figure 4B). The attenuation of HP inputs following PFC stimulation required a burst of stimuli, suggesting this type of interaction among inputs may occur only during behavioral conditions in which the PFC is strongly activated.

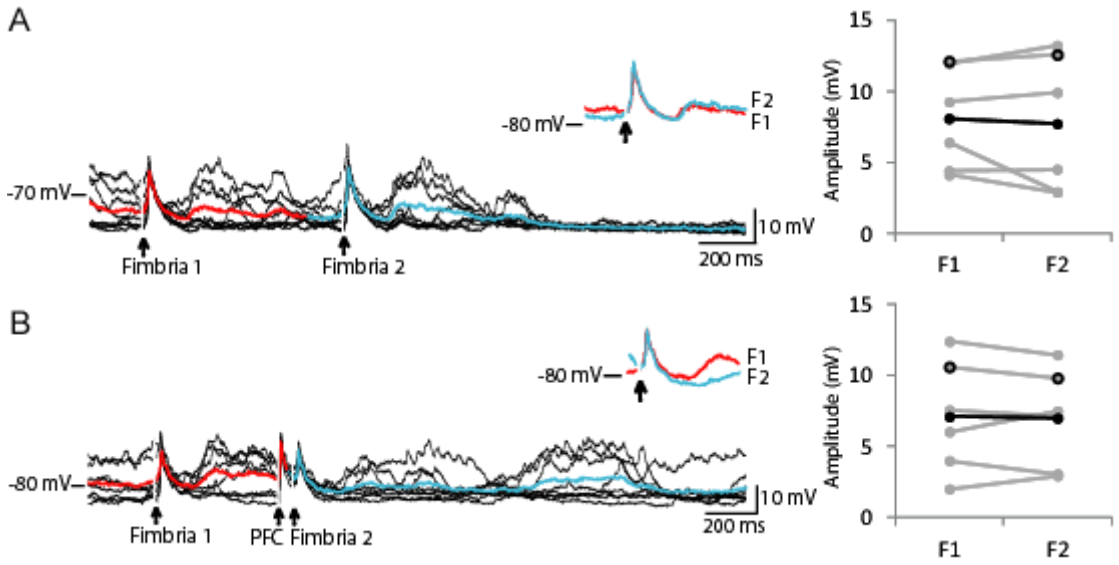

Figure 4. Fimbria-evoked EPSP suppression requires robust PFC activity
(A) Overlay of responses to F1 and F2 stimulation without the intervening PFC train stimulation. Mean responses to F1 and F2 are highlighted in red and blue, respectively, and overlaid in the inset. Right: Plot of all F1 and F2 values obtained in these conditions showing absence of a significant difference.
(B) Overlay of traces showing F1 and F2 responses with single-pulse PFC stimulation. MSNs responded with an EPSP to single pulse PFC stimulation, which did not significantly impact the F2 response. Inset shows overlay of average F1 (red) and F2 (blue) responses. Right: F1 and F2 amplitudes show absence of F2 attenuation 50 ms after a single PFC pulse.

II. *Specificity of Heterosynaptic Suppression in MSNs*

To assess whether PFC-evoked suppression of HP responses can be generalized to other inputs, I tested the effects of PFC train stimulation on MSN responses to thalamic afferent activation. The thalamus is an important source of glutamatergic afferents to the VS (Berendse and Groenewegen, 1990), which may also play a role in behavioral responses. Single-pulse thalamus stimulation evoked a 6.0 ± 2.6 mV EPSP with a 45.0 ± 17.8 ms time to peak. The amplitude of the thalamus-evoked EPSP was reduced to 0.7 ± 1.1 mV 50 ms following the last pulse in the PFC train ($t_{(9)}$ = 6.34; $p < 0.0002$; n = 10; Figure 5A), but not 500 ms following the PFC train ($t_{(8)}$ = -0.27; p = 0.80; Figure 5B). In all of the MSNs tested, the thalamus response was significantly attenuated 50 ms following the PFC train ($p < 0.01$ in 11/11 cells), whereas in all but three MSNs, the thalamus response was not significantly reduced 500 ms following the PFC train. As was the case with fimbria-evoked responses, this suppression did not occur when the PFC train was omitted ($t_{(5)}$ = -0.29; p = 0.79; Figure 5C), and could not be achieved using a single-pulse stimulus of the PFC ($t_{(6)}$ = 0.48; p = 0.65; Figure 5D). The suppression of the thalamus-evoked response was not due to the PFC-elicited depolarization, as the amplitude of the EPSP evoked by the second thalamic stimulation (T2) remained significantly attenuated compared with the thalamus-evoked EPSP recorded prior to PFC stimulation (T1) at depolarized membrane potentials ($t_{(4)}$ = 2.76; p = 0.05). These data suggest that strong PFC activation can elicit heterosynaptic suppression of multiple excitatory inputs to the VS.

To address whether heterosynaptic suppression in VS MSNs is an exclusive feature of strongly activated PFC inputs, I investigated whether PFC responses can in

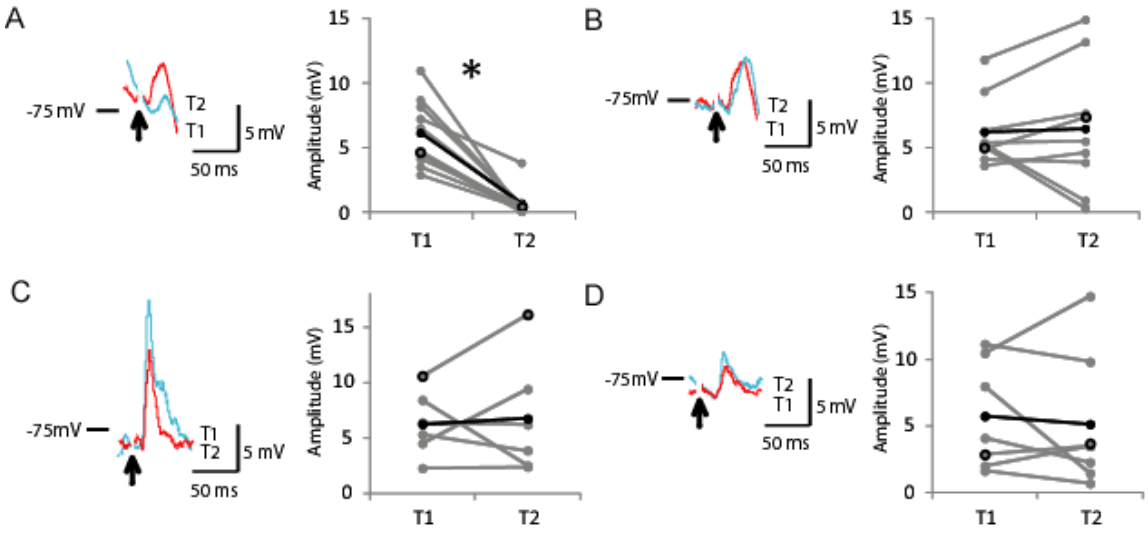

Figure 5. High frequency PFC stimulation suppresses thalamus-evoked responses at short, but not long latencies

(A) Average EPSPs evoked in a VS MSN by thalamus stimulation before (T1, red) and 50 ms after a 10 pulse, 50 Hz PFC train (T2, blue). Right: Plot of T1 and T2 amplitudes (gray: all neurons; closed black: average) showing a significant reduction following PFC train stimulation (* $p < 0.0002$, paired t test).

(B) In the same cell shown in *A*, the mean T2 (blue) amplitude is similar to T1 (red) 500 ms following the PFC train. Right: T1 and T2 values showing no difference.

(C) Average T1 (red) and T2 (blue) responses evoked in an MSN when no PFC stimulus was delivered. Right: Actual T1 and T2 values showing absence of attenuation.

(D) Average T1 (red) and T2 (blue) responses obtained from an MSN before and after single pulse PFC stimulation. Right: Plot of T1 and T2 amplitudes illustrating the absence of F2 response attenuation by single PFC pulses.

turn be subject to heterosynaptic suppression by strong activation of other glutamatergic inputs to the VS. I tested the impact of fimbria or thalamus train stimulation on EPSPs evoked by single-pulse PFC stimulation. Single-pulse PFC stimulation resulted in 11.3 ± 7.3 mV EPSPs in VS MSNs, with 18.3 ± 4.5 ms time to peak. A ten pulse, 50 Hz train stimulation of the fimbria failed to suppress PFC-evoked responses 50 ms after the final pulse in the fimbria train ($t_{(5)} = 0.41$; $p = 0.70$; Figure 6A). The same train delivered to the thalamus, however, reduced the amplitude of the PFC-evoked EPSP to 7.5 ± 6.7 mV ($t_{(6)} = 3.8$; $p < 0.01$; Figure 6B) without affecting the time to peak. The magnitude of suppression elicited by thalamus stimulation was much less than that elicited by PFC stimulation. Burst-like PFC stimulation reduced the amplitude of the fimbria-evoked response by 81.3 ± 15.4% and reduced the amplitude of the thalamus-evoked response by 89.0 ± 15.2%, whereas high frequency thalamus stimulation only reduced the PFC-evoked response by 37.0 ± 30.6%. In summary, PFC burst firing strongly attenuates HP and thalamic responses, strong thalamic activation has a moderate effect on PFC responses, and similarly strong activation of HP afferents does not diminish PFC responses. The data suggest that some, but not all, glutamatergic inputs to the VS affect responses evoked by other inputs by way of heterosynaptic suppression.

III. *$GABA_A$ Receptors Contribute to Heterosynaptic Suppression in MSNs*

As burst PFC stimulation activates VS local inhibitory processes (Gruber et al.,2009b), it is possible that local GABA neurotransmission contributes to the heterosynaptic suppression I report here. To assess this possibility, I included 200 μM picrotoxin in the intracellular solution for 22 cells from 15 adult male rats. As an open channel blocker at the $GABA_A$ receptor, picrotoxin can antagonize $GABA_A$ signaling

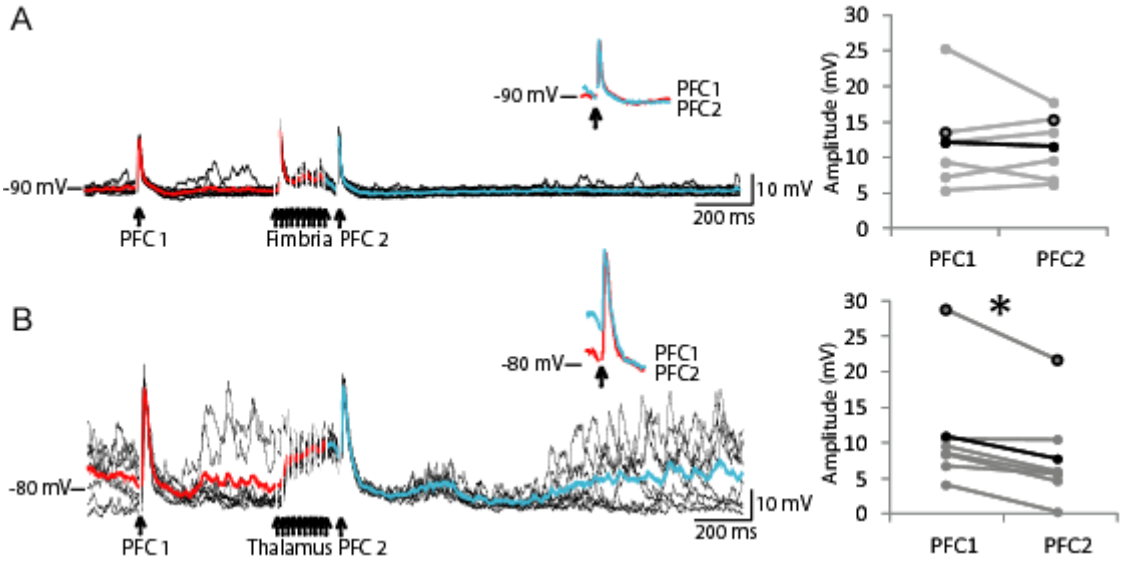

Figure 6. Effects of high frequency stimulation of the fimbria or thalamus on PFC-evoked responses in VS MSNs

(A) Overlay of traces showing PFC-evoked EPSPs before (PFC 1) and 50 ms after (PFC 2) stimulation of HP afferents with a 50 Hz, 10 pulse train. Inset shows mean PFC 1 (red) and PFC 2 (blue) responses. Right: Plot of actual PFC1 and PFC2 values (gray) and their average (closed black) showing lack of modulation by the fimbria train.

(B) Overlay of traces showing PFC1 and PFC2 evoked responses before and 50 ms after a train of stimuli to the thalamus (10 pulses at 50 Hz), with the average responses shown in the inset. The plot to the right illustrates a significant suppression of PFC-evoked EPSPs in MSNs following strong thalamic activation (* $p < 0.01$, paired t test).

when applied outside or inside the cell membrane (Akaike *et al.*, 1985; Inomata *et al.*, 1988; Cupello *et al.*, 1991; Metherate and Ashe, 1993). I found that the presence of picrotoxin in the recording pipette impacted the baseline properties of recorded MSNs. MSNs treated with picrotoxin had similar resting potentials (-84.8 ± 7.6 mV), up state frequency (0.7 ± 0.2 Hz), and up state duration (470.8 ± 105.9 ms) to untreated cells. The up state amplitude, however, was altered by the presence of picrotoxin (66.6 ± 6.8 mV; $t_{(67)} = 2.7$; $p < 0.01$). Furthermore, the proportion of silent MSNs was reduced following picrotoxin treatment (7/22, 32%), and the spontaneous firing rate of active cells was enhanced relative to untreated cells (3.5 ± 3.5 Hz, range, 0.02 – 10.6 Hz; $t_{(31)} = 2.8$; $p < 0.05$; Figure 7A). This increase in baseline firing activity suggests that picrotoxin relieved some tonic inhibition normally exerted onto VS MSNs.

To assess whether $GABA_A$ antagonism reduced the PFC-driven suppression of the fimbria-evoked EPSP, I subjected picrotoxin treated cells to the stimulation protocol described above. Picrotoxin did not significantly alter the F1-evoked EPSP, which had an amplitude of 8.5 ± 6.4 mV and a time to peak of 28.8 ± 6.9 ms. In the presence of picrotoxin, PFC train stimulation evoked sustained depolarizations similar to those elicited by the train in the absence of picrotoxin, however a greater percentage of MSNs fired action potentials during the PFC train (6/12; 50%). Following picrotoxin administration, the amplitude of the F2-evoked response 50 ms after the PFC train was still reduced relative to that of the F1-evoked response ($t_{(11)} = 2.4$; $p < 0.05$; Figure 7D); the F2 response was significantly attenuated in all but one of the recorded MSNs ($p < 0.05$ in 8/9 cells). The magnitude of that suppression, however, was reduced compared to the magnitude of suppression under baseline conditions; as stated above, the PFC train

reduced F2-evoked responses by 81.3 ± 15.4% in the absence of picrotoxin, whereas in the presence of picrotoxin, the magnitude of suppression was reduced to 49.6 ± 52.2%. The median magnitudes of suppression without and with PTX were 75.9% and 67.8%, respectively; the distributions in the two groups differed significantly (Mann-Whitney $U = 128$, $n_1 = 14$, $n_2 = 12$, $P < 0.05$ two tailed; Figure 7E). These findings suggest that $GABA_A$ mediated inhibition contributes to the suppression of fimbria evoked EPSPs following the PFC train, but does not account entirely for this suppression.

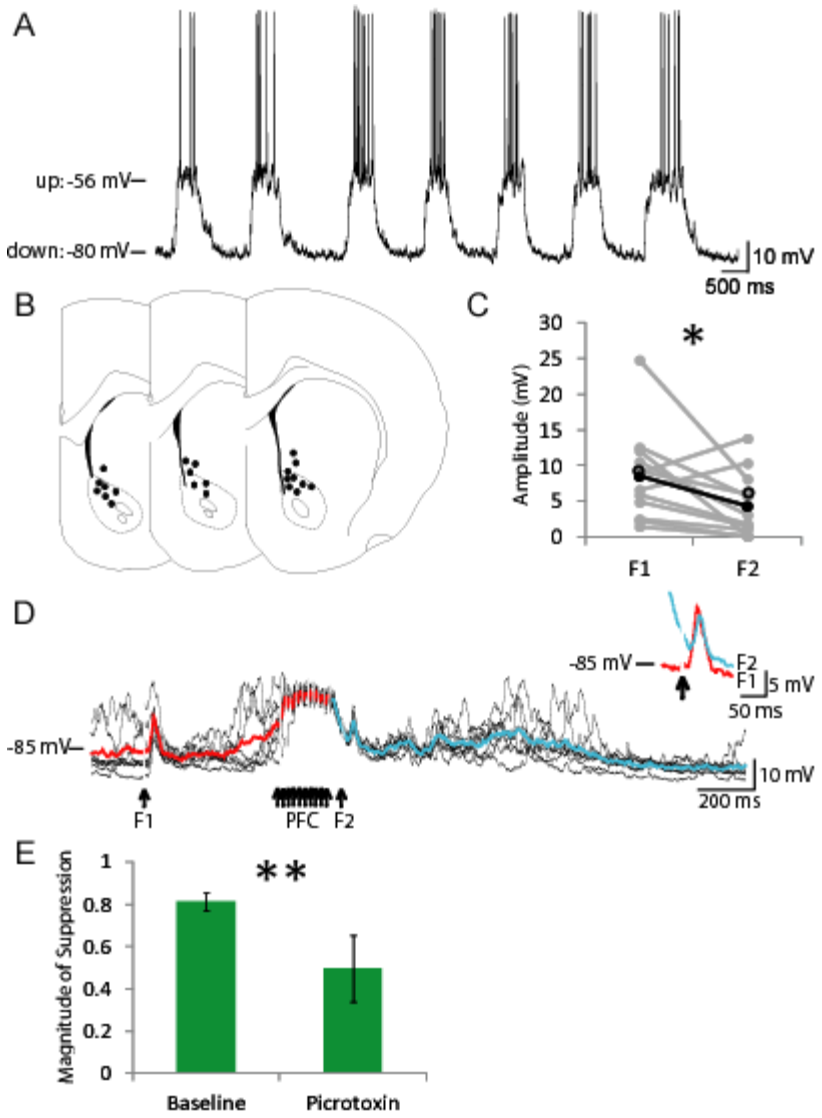

Figure 7. Picrotoxin alleviates some, but not all, of the PFC-mediated suppression of EPSPs in VS MSNs

(A) Representative trace showing increased spontaneous firing in an MSN recorded with 200 μM picrotoxin in the intracellular solution. This cell transitioned to the upstate at a frequency of 0.7 Hz and fired at 2.4 Hz.

(B) Illustration of recording sites in the VS using picrotoxin. Recorded cells fell within the same regions recorded without picrotoxin.

(C) Actual amplitude values of all F1 and F2 evoked responses recorded with picrotoxin in the intracellular solution (gray), and their average (closed black) indicating an overall suppression of F2 (* $p < 0.05$; paired t test). Open black circles indicate the example shown in the (D).

(D) Overlay of responses to fimbria stimuli before and 50 ms following train PFC stimulation following picrotoxin treatment. Mean responses to F1 and F2 are highlighted in red and blue, respectively, and overlaid in the inset.

(E) Plot comparing the magnitude of suppression of the F2 response 50 ms following PFC train stimulation under baseline conditions and in the presence of picrotoxin. Picrotoxin reduced the magnitude of PFC-elicited suppression (** $p < 0.05$; two tailed Mann-Whitney *U*).

Discussion

I found that high frequency PFC stimulation suppresses EPSPs arising from single-pulse fimbria stimulation in VS MSNs. This suppression was observed at a short latency following the PFC stimulus (50 ms after the final pulse in a 10 pulse, 50 Hz train delivered to the PFC), but not at a long latency (500 ms) following the PFC train. The suppression of fimbria-evoked EPSPs by the PFC cannot be attributed solely to the depolarization of recorded cells elicited by the PFC train, as fimbria-evoked EPSPs were not attenuated by the depolarization elicited by spontaneous up states or current injection through the recording electrode. Moreover, burst-like activation of the PFC was necessary to produce suppression of fimbria responses; single-pulse stimulation of the PFC did not reduce the magnitude of the fimbria-evoked EPSP. The suppression of glutamatergic responses by robust PFC activation extended to other afferents as well, as PFC train stimulation attenuated thalamus-evoked responses. Trains of stimuli to the HP did not attenuate PFC-evoked EPSPs, consistent with the proposed gating relationship of the HP with VS MSNs (O'Donnell and Grace, 1995). Burst-like stimulation of the thalamus, however, was able to attenuate the PFC-evoked response, but this effect was not as dramatic as the near-total suppression of HP and thalamic inputs caused by PFC train stimuli. These data suggest that burst-like PFC activity elicits brief heterosynaptic suppression of HP and thalamic inputs to the VS, and further indicate that hippocampal gating can be transiently interrupted by strong PFC activation.

The integration of excitatory inputs in the VS is complex, with several non-linearities (Goto and O'Donnell, 2002; Wolf et al., 2009). HP afferents are critical for the spontaneous up states observed in anesthetized animals; VS up states are eliminated if the

fimbria/fornix is transected or inactivated (O'Donnell and Grace, 1995) and can be detected simultaneously with HP spindles (Goto and O'Donnell, 2001b). As MSNs fire action potentials only from the up state, the relationship of the HP to the VS has been described as a gating mechanism, in which the VS must receive convergent excitatory input from the HP for other excitatory inputs, including those from the PFC, to be transmitted onward to downstream targets (O'Donnell and Grace, 1995). The critical role of the HP in shaping VS activity is also apparent in the behaving animal. Under resting conditions, the VS shows highly synchronous field potential activity with the ventral HP (Gruber et al., 2009a). Furthermore, place cells are found in the VS (Lavoie and Mizumori, 1994), and their activity is likely driven by HP inputs. These findings indicate that the HP gating of other inputs is a default mode of input integration by which contextual information is continuously updated in the VS.

I. *Robust PFC Stimulation Evokes Heterosynaptic Suppression in the VS*

The strong HP influence over VS activity is not insurmountable, however. During behavioral conditions that require PFC involvement, brief burst-like firing of PFC pyramidal neurons results in an instantaneous frequency in the population that can exceed 50 Hz (Chafee and Goldman-Rakic, 1998; Peters et al., 2005). Here, I found that PFC stimulus trains mimicking naturally occurring burst activity transiently suppress other inputs, including those arriving from the HP. In the behaving animal, decision making epochs are marked by transient VS synchrony with the PFC. During these epochs, VS-HP coherence in the theta frequency band is reduced despite the persistence of strong theta activity in the HP (Gruber et al., 2009a). These data suggest that the PFC can

commandeer control of VS activity during brief periods of high PFC activity. The fact that this transiently enhanced PFC-VS synchrony occurs in the face of unchanged HP activity suggests the interaction must take place within the VS. Here, I demonstrate that the PFC is capable of suppressing synaptic responses evoked by other inputs if, and only if, the PFC is strongly activated.

VS responses to HP and thalamic inputs are transiently suppressed by burst-like PFC activation in a manner that does not depend on depolarization. Although the PFC-evoked up state could attenuate HP and thalamic EPSPs by virtue of their occurring at a depolarized membrane potential, I found that the suppression persisted even if the post-PFC responses were compared to EPSPs recorded at the same membrane potential range. The experiments in which MSNs were artificially depolarized may be confounded by the limited space clamp of the recording configuration that limits the effective depolarization to very proximal sites; if the interactions that drive the observed suppression are more distal, somatic current injection is unlikely to affect the first EPSP. However, the cases in which the first HP- or thalamus-evoked EPSP was measured during spontaneous up states circumvent this confound, as up states are synaptically driven and also present in dendrites (Wolf et al., 2005). These data strongly argue for the absence of a membrane depolarization effect in the suppression I observed.

PFC train stimulation paradoxically evokes silent, activated states in VS MSNs. Despite producing a persistent depolarization in these neurons, trains of stimuli to the PFC do not result in action potential firing in the majority of the population (Gruber and O'Donnell, 2009). Here, burst PFC stimulation evoked action potentials in only 14% of recorded VS neurons. This finding of limited MSN activation by PFC burst stimulation is

comparable to the small percentage of MSNs showing c-fos activation by drug-associated cues in a learning paradigm (Koya et al., 2009). One interpretation of these data is that the strong PFC activation required to guide goal-directed behaviors is likely encoded in a discrete distributed ensemble of VS neurons. For signals from the PFC to be effectively relayed through sparse ensembles in the basal ganglia, it is essential to suppress irrelevant and competing neural activity. The heterosynaptic suppression elicited by PFC trains of action potentials may blunt excitatory activity in MSNs for a brief period following the PFC burst, allowing for the activation of spatially and temporally restricted sparse neural ensembles.

II. ***Mechanisms Responsible for Heterosynaptic Suppression in the VS***

Several mechanisms are potentially responsible for the heterosynaptic suppression I observed in the VS. Activation of local fast-spiking GABAergic interneurons stands out as a strong possibility, as this cell population is highly activated by train PFC stimulation and produces feed-forward inhibition of PFC responses (Mallet *et al.*, 2005; Taverna *et al.*, 2007; Gruber and O'Donnell, 2009; Gruber *et al.*, 2009b). I found that intra-MSN $GABA_A$ blockade reduced the extent of heterosynaptic suppression of HP inputs by PFC activation. This finding suggests that synaptic inhibition of MSNs contributes to the suppression of EPSPs following PFC train stimulation. As intracellular diffusion of PTX from high-resistance electrode tips may be limited to proximal sites, this manipulation likely underestimates the role of $GABA_A$ receptors in producing heterosynaptic suppression in VS MSNs. Furthermore, local interneurons are not the only potential source of inhibition over MSNs given that the suppression results from shunting of

synaptic responses in MSNs at least partly by way of GABAergic signaling. MSNs also inhibit neighboring MSNs through chemical and electrical synapses (O'Donnell and Grace, 1997). While it is possible that recurrent inhibition of recorded neurons by neighboring MSNs resulted in the observed suppression of responses, this alternative seems unlikely as surround inhibition among striatal MSNs is comparatively weak (Jaeger *et al.*, 1994; Tunstall *et al.*, 2002; Koos *et al.*, 2004).

Other potential mechanisms accounting for the heterosynaptic suppression in VS MSNs include molecules that can be produced postsynaptically and affect presynaptic terminals. In the VS, extensive data indicate endocannabinoids acting on CB1 receptors may reduce glutamate and GABA release (Lovinger and Mathur, 2012), possibly serving as mediators of the findings reported here. The case for CB1 receptors is not strong, however, as the heterosynaptic suppression reported here would require endocannabinoids to be released by MSNs upon PFC bursting and act upon HP and thalamic inputs. Although corticostriatal synapses are inhibited by presynaptic CB1 receptors, there is no evidence that HP afferents are similarly inhibited. Furthermore, endocannabinoid action in the striatum also functions to suppress inhibitory input to MSNs, which could oppose the effect reported here. Another candidate for producing heterosynaptic suppression in the VS is opioid signaling. A subset of VS MSN contains dynorphin (Svingos et al., 1999), which upon release can act on presynaptic kappa receptors, reducing glutamate release (Hjelmstad and Fields, 2001; Hjelmstad and Fields, 2003). Activation of dopamine receptors represents another possible mechanism for the observed heterosynaptic suppression. Stimulation of presynaptic D2 receptors has been reported to reduce glutamate release from excitatory afferents (O'Donnell and Grace,

1994), however a PFC-evoked increase in dopamine release would require activation of VTA neurons and thereby necessitate a longer latency to onset and duration of suppression than those observed here. Moreover, dopamine release in the striatum would also be expected to increase firing in D1-expressing MSNs. Therefore, dopamine release is also an unlikely mechanistic candidate. Although my data suggest the possible participation of GABAergic synapses, the effect of $GABA_A$ blockade was weak, so it is likely that other mechanisms contribute to heterosynaptic suppression in the VS. Understanding the role of these modulators in the complex integration of information within the VS will help us establish synaptic mechanisms underlying behavioral response selection, determine whether they are involved in neuropsychiatric conditions, and eventually provide clues as to novel therapeutic approaches.

III. *Functional Consequences of PFC-driven Heterosynaptic Suppression in the VS*

Transient heterosynaptic suppression driven by strong PFC activity may facilitate transmission of PFC-related information by the VS through basal ganglia loops. Whereas HP inputs may subserve a critical gating function, the impact of burst-like PFC activity upon information processing in the VS is clearly distinct from that of HP activity. Behavioral studies indicate different functional impacts of PFC and HP inputs to the VS. For example, unlike limbic afferents to the VS, PFC stimulation does not elicit self-stimulation behavior (Stuber et al., 2011). This finding suggests that cortical inputs may have a qualitatively different connectivity in VS circuits than HP inputs, and that responses to convergent PFC and HP inputs may not be additive in the VS. I propose that suppression of HP responses by strong PFC activation may allow an efficient transfer of

PFC commands through basal ganglia loops and an unhindered selection of the appropriate behavioral response.

As the role of thalamic inputs to the VS is not well understood, the functional implications of the PFC-thalamic input interaction are unclear. Thalamic afferents arriving to striatal regions primarily originate in the nonspecific nuclei (Groenewegen and Berendse, 1994). These projections are therefore likely to be involved in a global activating function and perhaps in conveying crude sensory information. Transient suppression of this influence by strong PFC activation may facilitate the relay of PFC information through the VS with minimal disturbance from ongoing arousal state-related information.

The impact of bursts of PFC activity on VS physiology may be essential for supporting cognitive functions that depend on the PFC. The VS itself is critical for Pavlovian and instrumental behaviors, as reviewed above. PFC-VS interactions are critical for rodent decision-making (Christakou et al., 2004; St Onge et al., 2012), and are also important for human cognition. Deep EEG recordings during a reward-based learning task in humans reveal brief epochs of synchronous activity in the VS and medial PFC during decision making instances (Cohen et al., 2009). In addition to transiently enhanced PFC-VS activity, several studies indicate that interactions between the HP and VS vary during epochs that require decisions. Simultaneous local field potential recordings from both structures reveal that ventral HP-VS coupling is altered during performance of a T-maze task (Tort et al., 2008) and in cue-guided lever pressing (Gruber et al., 2009a). Overall, these data illustrate that behavioral conditions that require decisions are characterized by enhanced PFC-VS coordination and varied HP-VS

synchrony. The PFC-driven heterosynaptic suppression I report here may be responsible for the latter, thereby contributing to the VS output patterns that underpin executive functions. Indeed, a two-state scenario is plausible, wherein the HP-VS axis is dominant when an individual exploits known sources of reward, and the PFC commandeers the VS in cases requiring the exploration of new sources of reward.

Alterations to the PFC-VS projection have been implicated in neuropsychiatric disorders and addictive behaviors. For instance, synaptic responses and plasticity mechanisms in this pathway are affected in animals that self-administer cocaine (Luscher and Malenka, 2011). Moreover, impaired top-down control of drug seeking and self-administration by the PFC has been suggested to accelerate the transfer of these behaviors from goal directed to habit-mediated processes (Jentsch and Taylor, 1999; Everitt and Robbins, 2005). An altered PFC-VS interaction that elicits inadequate heterosynaptic suppression of limbic inputs could result in the activation of inappropriate neural ensembles, which could thereby result in the inability to suppress cue-driven, habitual drug-seeking. That is to say, a reduction in PFC mediated heterosynaptic inhibition may underly the proposed acceleration of habitual responding to drug-associated cues.

The contribution of disrupted PFC-mediated heterosynaptic suppression in the ventral striatum to other psychiatric disorders is also conceivable. Cognition and decision making are altered in schizophrenia, and in particular, individuals suffering from the disorder fail to adapt to changing environmental demands in order to meet their goals. This “perseveration” in decision making, in which actions that were previously rewarded persist after those actions no longer elicit reward, has been notably characterized in

schizophrenia using the Wisconsin Card Sorting Task (Fey, 1951). This and other cognitive abnormalities, including severe working memory deficits, compound the difficulties of treating and rehabilitating those who suffer from schizophrenia. It has been proposed that “noisy” or “inappropriate” activity in the PFC results in the symptoms of schizophrenia, in part through the influence of the PFC on ventral striatal activity (O'Donnell and Grace, 1998). Such hyperactivity in the PFC could aberrantly increase heterosynaptic suppression in the ventral and dorsomedial striata, thereby interfering with their normal functions to support goal-directed decision making and appropriate action selection.

The nonlinear interactions among inputs to VS MSNs such as the PFC-mediated heterosynaptic suppression of synaptic responses described here may be critical for shaping appropriate behavioral responses. My observation that heterosynaptic suppression of hippocampal inputs to the VS can be driven during epochs of high PFC activity suggests that targeting this mechanism may be useful for enhancing cognitive functions. In this regard, the likely involvement of local GABA processes indicates that GABA pharmacology may prove beneficial in treating certain psychiatric conditions. Therefore, the manipulation of these interactions may provide novel therapeutic approaches for disorders in which decision-making is impaired.

IV. ***Conclusion: Closing the Gate in the Limbic Striatum***

Considered together, the findings I present here suggest that the Gating Hypothesis does not adequately explain information processing in the VS. Rather than requiring activation by the HP in order to conduct signals onward to the pallidum, MSNs

of the VS act as sensitive detectors of patterns of activity within their diverse afferents. In this way, the VS is less of a gated structure which must be opened for information to pass, and more of a switchboard capable of directing activity based upon complex and ever-changing input signals. The notion of the NAc as a switchboard represents an advance in thinking about the ways in which this important brain region handles diverse, convergent input, and will potentially inspire novel hypotheses about the dynamic nature of reward related information processing in health and disease.

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