Control of Functional Connectivity in Cerebral Cortex by Basal Ganglia Mediated Synchronization

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Abstract

Since the earliest electroencephalography experiments, large scale oscillations have been observed in the mammalian brain. In more recent studies they have been identified not only in the cerebral cortex and thalamus, but pervasively in the healthy basal ganglia. While correlations with stimuli, behavior, and mental states have long been recognized, the precise function of these oscillations has often been mysterious, particularly in the basal ganglia. In this paper, I propose the basal ganglia mediated synchronization model to help explain many of these correlated oscillatory phenomena, relating stimulus-response and reinforcement mechanisms to associative synchrony mechanisms. In this model, patterns of activity in cortex stimulate striatal responses whose spike timing precisely reflects that prevailing in the input pattern. These responses are then recirculated in closed and open loops, chiefly via the thalamus, to the feedback-recipient layers of cortex, where they selectively establish and reinforce effective connections by controlling spike-timing-dependent gain. Corticostriatal and striatonigral conduction delays are critical to this mechanism, and evidence suggests that these delays are unusually long, and unusually varied, in arrangements that might facilitate learning of useful time alignments. Structural arrangements in the basal ganglia show further specialization for this role, with convergence in the inputs from cortex, and divergence in many of the return paths to cortex, that systematically reflect corticocortical anatomical connectivity. The basal ganglia also target the dopaminergic, cholinergic, and serotonergic centers of the brainstem and basal forebrain, and the reticular nucleus of the thalamus, structures broadly implicated in the modulation of oscillatory network activity and expressions of plasticity. The basal ganglia also target the dopaminergic, cholinergic, and serotonergic centers of the brainstem and basal forebrain, and the reticular nucleus of the thalamus, structures broadly implicated in the modulation of oscillatory network activity and expressions of plasticity. The basal ganglia, by learning to coordinate these various output channels, are positioned to facilitate and synchronize activity in selected areas of cortex, broadly impart selective receptivity, attenuate and disconnect interfering activity, and recurrently process the resulting patterns of activity, channeling cognition and promoting goal fulfillment. Dysfunctions in the components of this highly distributed system are associated with syndromes of perception, cognition, and behavior, notably the schizophrenias, some or all of which might fundamentally be disruptions of basal ganglia mediated synchronization.

Keywords: basal ganglia, convergence-divergence, thalamus, intralaminar, thalamocortical, cerebral cortex, synchrony, spike timing, entrainment, selection, functional connectivity, large scale networks, iteration, consciousness, schizophrenia

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1. Introduction and Overview

The cerebral cortex has long been styled the seat of higher thought, due to its size and disproportionate growth in mammalian phylogeny (Mountcastle 1998), and its astronomically large dimensionality (Tononi 2004). But that size and dimensionality necessitate an exquisitely powerful coordination mechanism. In this paper, I develop the hypothesis that the basal ganglia are fundamental to that mechanism.

Specifically, this paper introduces a new model of mammalian basal ganglia (BG) function, basal ganglia mediated synchronization (BGMS), implicating the BG extensively in the dynamic regulation of functional connectivity in the cerebral cortex, by spike-timing-dependent gain control within the areas they target. As detailed throughout this paper, the BGMS model helps explain several historically mysterious aspects of BG and related physiology, among them:

- Unusually long and diverse delays, temporally inverted spike-timing-dependent plasticity, and unusually high convergence and divergence, of paths through the BG;
- Special sensitivity in the striatum to large scale synchronies, large scale oscillatory synchronies spanning BG components, and striatal oscillations that induce synchronous cortical oscillations;
- Rapid statistically independent tonic discharge by projection neurons in BG output structures;
- Large scale lateral inhibition in the basal ganglia, producing selections;
- Widespread, diffuse projections from the intralaminar nuclei of the thalamus to cortex, loss of consciousness from inactivation of these nuclei, and particular intimacy of these nuclei with the BG;
- The function of corticothalamic projections;
- Stereotyped rhythmicity of spiking in effective corticomotor signaling;
- Paradoxical results from lesions of BG output structures, and permanent loss of normal consciousness by their bilateral destruction;
- Dense integration into BG circuitry of highly associative and abstractly cognitive areas of cortex; and
- The etiology and ontology of schizophrenia.
All of these phenomena are, in principle, explained by the proposition that the intact BG recognize and select useful large scale patterns of synchronized cortical activity, and route the predominant oscillations within them, chiefly via the thalamus, back to cortex, where they reinforce and further synchronize activity contributing to the selected patterns, and broadly promote precisely discriminative receptivity to selected activity. This proposal implies that the BG are essential organizers of cortical activity.

In this section:

1.1. The basal ganglia resolve conflicts and ambiguities by making selections informed by goals, context, and expectation.
1.2. Population spike time relations are a pervasive mechanism for selective effective connectivity.
1.3. Synchronies are crucial in perception, cognition, behavior, and pathology.
1.4. The thalamus can control cortical oscillation and corticocortical synchronies.
1.5. The thalamus is in an ideal position to control large scale cortical synchronies.
1.6. The basal ganglia form loops with cortex that reflect cortical patterns of connectivity and parallelism.
1.7. The basal ganglia are arranged to participate in the regulation of oscillatory activity in large scale thalamocortical networks.
1.8. The physiology of the basal ganglia, thalamus, and cortex, suggest that the basal ganglia can mediate synchronization in cortex.

1.1. The basal ganglia resolve conflicts and ambiguities by making selections informed by goals, context, and expectation.

One particularly durable account of BG function is that they serve as a selection mechanism, resolving conflicting or ambiguous claims on computational and behavioral resources (Redgrave et al. 1999; Mink 1996; Graybiel 1998; Stephenson-Jones et al. 2011; Hikosaka et al. 2000). Similarly, the BG have been modeled as controllers of gates in cortex, selectively facilitating motor output (Chevalier and Deniau 1990; Hikosaka et al. 2000) and establishing contextually appropriate items in working memory (Frank et al. 2001; O’Reilly and Frank 2006).

At a more fundamental level, the BG are thought to develop a repertoire of compound stimulus-response relations through reinforcement learning, ultimately forming habits (Graybiel 1998, 2008). In this view, the BG transform cortical and subcortical inputs representing goals, elaborately contextualized by other cortical and subcortical inputs representing environmental state and recent history, into spatiotemporally complex, precise, widely distributed, often sequential adjustments to brain state, that are expected to promote internal and external (environmental) changes in fulfillment of those goals. It has been previously suggested that a fundamental facility of the BG for precisely and flexibly triggered, structured, and directed neurodynamic gestures has far-reaching consequences (Graybiel et al. 1994; Graybiel 1997). This facility is at the heart of the proposal advanced here, because—as reviewed below—effective connectivity among the targets of the BG is strongly associated with the precise timing relationships of the activity within them.

1.2. Population spike time relations are a pervasive mechanism for selective effective connectivity.

According to this proposal, the BG and thalamus establish and reinforce effective connections in cortex by distributing precisely synchronized spike volleys to its feedback-recipient layers, imparting discriminative receptivity by spike-timing-dependent gain control. The proposition that spike synchronies are correlates of functional and effective connectivity, and represent associations, is supported by an array of evidence and integrative theory (von der Malsburg 1981, 1999; Bastos et al. 2015; Bressler 1995; Damasio 1989; Fries 2005; Friston 2011; Hutchison et al. 2013; Kopell 2000; Meyer and Damasio 2009; Siegel et al. 2012; Singer 1993, 1999; Singer and Gray 1995; Varela et al. 2001; Wang 2010). Theta (~4-8 Hz), beta (~15-30 Hz), and gamma (~30-80 Hz) oscillations are most prominent in these mechanisms (Wang 2010).

Aggregate oscillations in the brain have been known for nearly a century by electroencephalography (EEG), one of the earliest techniques for measuring brain function directly (Berger 1929; Jasper 1937). EEGs measure the surface voltage fluctuations that result from the extracellular summation of phase-correlated electrical activity within large populations of neurons, mostly in the cerebral cortex (Buzsáki et al. 2003, 2012; Olejniczak 2006). Phase-correlated activity in smaller populations of neurons can be characterized through the resulting local field potentials (LFPs), measured with implanted electrodes (Buzsáki et al. 2012), and fluctuations in the LFP are a strong proxy for the membrane potentials in the individual neurons near an electrode, and for the synaptic currents that contribute to them (Haider et al. 2016).
Synchronizability of populations of neurons follows from the characteristics of individual neurons. Physiologically realistic simulations suggest that synchronous spike volleys can propagate coherently through a succession of many directly linked neurons (Diesmann et al. 1999), and activity-driven plasticity mechanisms are crucially dependent on relationships of temporal coincidence among individual spikes and spike bursts (Song et al. 2000; Gerstner et al. 1996). Moreover, finite and diverse conduction delays, apparent in the fiber populations of biological neural networks, have been shown in simulations to provide for combinatorial coverage, notionally infinite dimensionality, and correspondingly stupendous representational capacities (Izhikevich 2006).

1.3. Synchronies are crucial in perception, cognition, behavior, and pathology.

Synchronies are pivotal in perceptual processing. For example, the relationship of oscillatory frequency and phase in interconnected sensory areas, measured by LFPs, has been shown to strongly influence their effective connectivity (Womelsdorf et al. 2007), and the resolution of competitions among sensory inputs can be predicted from the relationship of the LFP frequency and phase within each input to those prevailing within their common target (Fries et al. 1997, 2002). Attentional orientation is accompanied by LFP synchrony between frontal and posterior cortex, characterized by strong frontally initiated beta or strong posteriorly initiated gamma synchrony in top-down and bottom-up orientation respectively (Buschman and Miller 2007). Some long range synchronies implicating prefrontal cortex (PFC) are associated with functional disconnection, manifesting as selective inattention (Sacchet et al. 2015).

Synchronies are also pivotal in the generation of behavior. Long range synchronies can be strongly predictive of behavioral decisions (Verhoef et al. 2011), and planning and execution of voluntary movements are associated with characteristic synchronization of activity in shifting ensembles of neurons in primary motor cortex, separate from changes in their firing rates (Riehle et al. 1997). Indeed, some of the gesture selectivity of activity in motor neurons is apparent only in their synchronies (Hatsopoulos et al. 1998).

In humans, the large scale architecture of neural synchronies has clear developmental correlates. Childhood improvements in cognitive performance are accompanied by increases in neural synchrony, while adolescence is accompanied by a temporary reduction in performance and synchrony, followed by oscillatory reorganization and still higher performance and synchrony in adulthood (Uhlhaas et al. 2009). The functional prominence of temporal precision is suggested by a finding that temporal acuity and psychometric g (a measure of general cognitive performance) covary, with g predicted significantly better by acuity than by reaction time (Ramsmsayer and Brandler 2007). Similarly, uniformity of cadence in successive gestures within a self-paced rhythm task correlates significantly with performance on a test of general intelligence (Madison et al. 2009).

Characteristic synchronal abnormalities are associated with diseases such as schizophrenia (Sz), autism, Alzheimer’s, and Parkinson’s (Uhlhaas and Singer 2006, 2012; Hammond et al. 2007), and the reorganization of synchronal architecture in adolescence may be the trigger for the onset of Sz in those at risk (Uhlhaas and Singer 2010; Uhlhaas 2013). Sz in particular is associated with pervasive physiological disruptions of the mechanisms underlying the generation and regulation of, and responses to, spike synchronies and functional connectivity (Friston and Frith 1995; Uhlhaas 2013; Pittman-Polletta et al. 2015), and multifariously implicates the BG (Robbins 1990; Graybiel 1997; Simpson et al. 2010; Wang et al. 2015; Grace 2016; Dandash et al. 2017; Mamah et al. 2007). Indeed, abnormal judgment in Sz of time intervals and sensory simultaneity (Martin et al. 2013; Schmidt et al. 2011; Ciullo et al. 2016), and highly significant motor deficits in Sz, on tasks as simple as rapidly alternating finger taps (Silver et al. 2003), give further evidence of common timing-related mechanisms underlying sensory, motor, and cognitive processing.

1.4. The thalamus can control cortical oscillation and corticocortical synchronies.

Much of the large scale oscillatory activity in cortex is not purely intrinsic, and directly implicates subcortical structures, particularly the thalamus. The thalamus is a major target of BG output (Haber and Calzavara 2009), and the proposition that the BG have a prominent role in controlling long range cortical synchronies follows in part from evidence that the thalamus performs this function. It has been shown clearly that the thalamus can control cortical oscillatory activity (Poulet et al. 2012), and that it can orchestrate lag-free (zero phase shift) long range synchronies in cortex (Ribary et al. 1991; Vicente et al. 2008; Saalmann et al. 2012). “Desynchronization” associated with mental activity in fact consists of focal, high-frequency (20-60 Hz) synchronization of distributed thalamocortical ensembles (Steriade et al. 1996). Long distance, multifocal (posterior visual, parietal, and frontal motor), lag-free synchronies in the beta band have been observed in association with visuomotor integration (Roelfsema et al. 1997), and similar lag-free beta synchronies, and precise antisynchronies, have been observed among loci in prefrontal and posterior parietal cortex in a visual working memory task (Dotson et al. 2014).

Projection by single thalamic nuclei to widely separated but directly interconnected cortical areas has
been noted (Goldman-Rakic 1988; Saalmann et al. 2012), and there is evidence that intralaminar thalamocortical projections systematically reflect corticocortical connectivity, with individual axons branching multiregionally (Kaufman and Rosenquist 1985a; Van der Werf et al. 2002). The hypothesis has been advanced that midline and intralaminar thalamic nuclei in particular are the hub of a system to control cortical synchronies and associated effective connectivity (Saalmann 2014; Purpura and Schiff 1997), and it has been demonstrated that the mediodorsal nucleus can control sustained functional connectivity in PFC (Schmitt et al. 2017). Indeed the entire population of calbindin-positive neurons in the thalamus has been proposed to function in this fashion (Jones 2001).

As detailed later, the interaction of physiologically distinct but spatiotemporally coincident inputs to cortex from intralaminar and non-intralaminar thalamus is a key mechanism within the model proposed here. In this mechanism, intralaminar thalamic projections act as a broadcast signal imparting highly selective receptivity and reinforcement, characterized by spatial diffusion and high temporal specificity, while non-intralaminar projections reinforce activity in specifically delineated predominantly frontal cortical areas, with much less temporal specificity. These distinct inputs to cortex interact with intrinsic cortical activity, arranging for rapid and dynamic recruitment of specific, contextually appropriate large scale cortical networks.

1.5. The thalamus is in an ideal position to control large scale cortical synchronies.

Thalamic control of cortical oscillation and synchronies follows naturally from the developmental relationship of thalamus to cortex. While a ballet of intrinsic prenatal processes parcels the cortex into its major cytoarchitectonic areas (Rakic 1988), thalamocortical axons reach their pallial destinations before neurogenesis and migration of the receiving cortical neurons (López-Bendito and Molnár 2003; Paredes et al. 2016), and the basic architecture of cortex is thought to develop partly in response to patterns of activity in these axons (Katz and Shatz 1996). “Developmental exuberance”, entailing the robust proliferation of ephemeral long range links in cortex, is followed by a postnatal paring process driven in part by early patterns of thalamocortical activity (Innocenti and Price 2005; Price et al. 2006).

The manipulation of thalamocortical input patterns can dramatically alter cortical physiology and function (Rakic 1988). For example, uniquely visual attributes can be induced in cortical areas that normally subserve audition by rerouting retinal inputs to the thalamic auditory nuclei (Sharma et al. 2000).

These roles establishing the anatomical connectivity and intrinsic function of cortex position the thalamus uniquely to regulate cortical functional connectivity.

The thalamus is also uniquely positioned anatomically, at the base of the forebrain on the midline. This is an optimal situation for distributing synchronized spike volleys to far-flung loci in cortex. It is striking that postnatally (week 4 in mice), the thalamocortical projection to a given functional area of cortex develops a uniform delay, in many areas less than 1 ms of maximum disparity, despite widely varying axon lengths; even intermodally, thalamocortical delays are often aligned within 2-3 ms (Salami et al. 2003; Steriade 1995). The central clustering of thalamic nuclei is noteworthy in itself: absent functional requirements and associated evolutionary pressures to the contrary, many of these nuclei might migrate toward the cortical areas with which they are intimate, realizing physiological efficiencies (Scannell 1999). Moreover, in many mammals the dorsal BG maintain rough radial symmetries centered on the thalamus, suggesting time alignment pressures like those that appear to influence the gross anatomy of the thalamus.

1.6. The basal ganglia form loops with cortex that reflect cortical patterns of connectivity and parallelism.

It has long been appreciated that the cortex, striatum, pallidum/substantia nigra, and thalamus are arranged in loops placing each under the influence of the others (Alexander et al. 1986; Parent and Hazrati 1995a; Middleton and Strick 2000). As reviewed in detail later, the pyramidal neurons of cortical layer 5 (L5) originate the primary input to the BG “direct path” centrally implicated in these loops, and are among the recipients of the output from the direct path via the thalamus. While subdivision of these loops into parallel circuits and constituent channels has been noted (Alexander et al. 1986, 1991), in toto the pathways of the BG exhibit remarkably varied patterns of convergence, divergence, and reconfiguration (Joel and Weiner 1994; Hintiryan et al. 2016).

Diffuse projection fields from wide areas of cortex exhibit high convergence-divergence, and are proposed to supply extensive context throughout the striatum (Calzavara et al. 2007; Mailly et al. 2013). Projections from interconnected cortical regions, including reciprocally interconnected pairs of individual neurons, systematically converge and interdigitate in the striatum (Van Hoesen et al. 1981; Selemon and Goldman-Rakic 1985; Parthasarathy et al. 1992; Flaherty and Graybiel 1994; Lei et al. 2004; Morishima and Kawaguchi 2006; Hintiryan et al. 2016), and projections from interconnected areas have been shown to converge on individual fast spiking interneurons (FSIs) (Ramanathan et al. 2002). These arrangements show that the BG are particularly concerned with corticocortical connectivity. Even before much of this evidence was uncovered, it was suggested that arrangements of convergence and interdigitation in the corticostriatal projection position the striatum to integrate,
compare, or synchronize neural computations in distant areas of cortex (Mesulam 1990).

By having a sharp view of afferents from directly interconnected areas, simultaneous with a diffuse view of more widespread cortical activity, a striatal neighborhood is supplied with information upon which appropriate corticocortical connectivity decisions might be made as a function of present connectivity and context, with particular expertise for the functional domains implicated by those focal afferents. Crucially, a striatal neighborhood innervated by multiple cortical areas can impart oscillation from one of them to the others, through open loops back to cortex, with particular significance for directly interconnected areas. Meanwhile, partial segregation of channels through the BG likely facilitates parallel processing of operations that require only partial coordination, with the degrees and directions of segregation tending to reflect the degrees and directions of non-interference and independence.

Parallelism in the BG provides for the simultaneous processing in the striatum of activity at multiple oscillatory frequencies in distinct regions, associated with distinct domains of skill acquisition and performance, with distinct expressions of plasticity in each region, and inter-regional coherence varying task-dependently (Thorn and Graybiel 2014). In cortex, too, evidence suggests that distributed functional networks are largely parallel, and entail interdigitation in circuit nodes, particularly in prefrontal and other associative areas (Goldman-Rakic 1988; Yeo et al. 2011; Livingstone and Hubel 1988), even while most areas have direct anatomical connections with each other (Markov et al. 2014). fMRI of spontaneous activity in resting humans has demonstrated corresponding integration, regionalization, and parallelism of cortico-BG networks (Di Martino et al. 2008).

1.7. The basal ganglia are arranged to participate in the regulation of oscillatory activity in large scale thalamocortical networks.

Prominent oscillatory activity in the BG, particularly beta oscillation, is associated with perception, attention, decision making, and working memory (Cannon et al. 2014), all of which implicate large scale brain networks. Sensitivity to widespread synchronies is intrinsic to striatal physiology (Zheng and Wilson 2002), and the BG-recipient thalamus projects densely to the striatum (Sidibé et al. 2002; McFarland and Haber 2000), so that dynamics and plasticity in the BG are driven in part by the synchronies present at their output.

The scope of BG influence on cortical activity is extensive, with artificial stimulation of the striatum affecting activity spanning the entire cerebral cortex (Lee et al. 2016). Large areas of the motor, limbic, association, and intralaminar thalamus are BG-recipient (Haber and Calzavara 2009; Groenewegen and Berendsse 1994; Sidibé et al. 2002; Smith et al. 2004), projecting to feedback-recipient layers in cortex, particularly L1, L3, and L5 (Clascá et al. 2012; Markov and Kennedy 2013). The widespread, perhaps comprehensive, influence of the BG on cortical activity suggests a general role, integral to the normal operation of cell assemblies throughout the neocortex.

There is evidence that projections from the BG-recipient thalamus to cortex are subject to coincidence detection (Llinás et al. 2002; Larkum et al. 2004; Volgushev et al. 1998) and lag-free lateral spread of oscillation (Tamás et al. 2000), and that the dynamics of these mechanisms are modulated by dopamine under direct BG control (Yang and Seamans 1996; Towers and Hestrin 2008). BG-facilitated burst firing in cortex might activate functional connections: Excitatory input from thalamus to the L1 dendrites of L5 pyramidal neurons, synchronous with deep layer inputs to those neurons, promotes burst firing (Larkum et al. 2004; Larkum 2013), while corticocortical bursts induce long range synchronization (Womelsdorf et al. 2014). BG input to the thalamus, affecting the temporal structure of activity there rather than its intensity, is crucial for a similar type of pallial burst generation in songbirds (Kojima et al. 2013).

Activity in the BG is time-locked to sensory and behavioral events, as implied by the model introduced here. For example, experiments in rats have demonstrated rapid, coherent oscillatory reset spanning the BG in response to sensory cues (Leventhal et al. 2012). Task-related oscillatory activity in the monkey BG correlates strongly with oscillation in the implicated areas of thalamus (Schwab 2016, chapter 5), and appears to induce phase-locked oscillation in prefrontal cortical areas (Antzoulatos and Miller 2014).

Habit learning is associated with the gradual emergence of widespread task-related spike synchronies in the striatum, suggesting shifts in the functional connectivity of the associated networks (Barnes et al. 2005; Howe et al. 2011). Indeed, in tasks with shifting stimulus-response contingencies, the human BG have been shown to establish appropriate functional connections between prefrontal and posterior visual cortex (van Schouwenburg et al. 2010b).

1.8. The physiology of the basal ganglia, thalamus, and cortex, suggest that the basal ganglia can mediate synchronization in cortex.

Drawing on these findings, I propose the basal ganglia mediated synchronization (BGMS) model, and detail its mechanistic components and their relations below. In the BGMS model, the BG learn to recognize salient patterns of distributed, phase-correlated cortical activity, responding with synchronized spike volleys with functionally optimal delays, relayed via the thalamus, to the feedback-recipient layers of other areas of cortex, and
back to those of the cortical areas of origin. These spike volleys reinforce activity in the areas of origin, promote activity in allied areas, and establish selective long range synchronies and consequent effective connectivity with other areas, both by elevating receptivity in the other areas by spike-timing-dependent gain, and—with stronger and more coherent activity—by promoting burst firing. This mechanism particularly implicates the structures of the direct path, with crucial and distinct roles for the long and diverse conduction delays of corticostriatial projections, for those of the striatopallidal and striatonigral projections, for the cortical projections of the motor and association nuclei of the thalamus, and for those of the intralaminar nuclei.

Structures associated with the BG “indirect” and “hyperdirect” paths are proposed to inhibit or desynchronize conflicting, aborted, irrelevant, and completed activity, consistent with functions already proposed and demonstrated for these structures (Smith et al. 1998; Parent and Hazrati 1995b; Schmidt et al. 2013; Lee et al. 2016). BG influences on dopaminergic, cholinergic, and serotonergic centers, and the thalamic reticular nucleus, are proposed to be coordinated with (and partly by) these direct and indirect path outputs, promoting activity that contributes to the selected effective connections, attenuating or functionally disconnecting activity that conflicts with them, and modulating the dynamics within effective connections, to promote gainful computation and motor output. These mechanisms also greatly influence the expression of plasticity in the implicated structures, orienting neurophysiological investments to favor salient stimuli and behaviors, aligning selections with expectations and goals, and improving the immediacy, precision, and thoroughness of those selections.

The physiological underpinnings of BGMS are narratively unwieldy. Crucial details span gross anatomy, hodology, microstructure, chemodynamics, electrotonus, and resultant computation and learning. Moreover, the architecture of the system entails multifarious looping, so that there is no natural beginning or end, and entails numerous bifurcations and remergences, so that even if a starting point is settled, there is no natural linear narrative. Thoroughness and clarity are thus somewhat mutually antagonistic and indeed, I fear, elusive. Moreover, divergence, convergence, and sparsity in the BG are so pervasive and extreme, that they seem optimized to conceal their operational essence in plain sight. In a sense, they likely are, to gracefully tolerate localized physiological insults. Functional description of the BG, more than of other major divisions of the vertebrate brain, has been fraught with these challenges throughout the history of neurology and neuroscience.

The approach I take here is the obvious—to review the physiology and function of the BG and thalamocortical systems, much of it established in studies conducted in previous decades, recontextualized to the BGMS model. Following the foregoing introduction, I begin with a discussion of the role posited for the BG in gating motor output, and the relevance of precision spike timing in that role, followed by a discussion of the general relationship of the BG to cortex and thalamus from a signal processing perspective. Following that, I review the areas of thalamus receiving BG direct path output, the areas of cortex receiving output from the BG via the thalamus, and some relevant physiological nuances of the implicated neurons and their connections. Following this are reviews of BG path delays and proposed delay plasticity mechanisms, and of the patterns of convergence and divergence in these paths, all fundamental to the BGMS model. Then I review in some detail the modulatory functions of dopamine, acetylcholine, and serotonin in the thalamocortical system, and BG influences over the release of these key neurotransmitters. Finally, I consider the roles of the BG in sensory perception and general cognitive coordination, and discuss some relationships and contrasts with the hippocampal, cerebellar, and other related systems.

Nearly a century ago, the eminent neurologist Kinnier Wilson remarked that the basal ganglia “still, to a large extent, retain the characteristic of basements-viz., darkness.” (Wilson 1925) Thanks to the profound exertions of a great many since then, much of this darkness has lifted, and we are now in a position to perceive the gear-like interlocking mechanisms by which the cerebral cortex, basal ganglia, and thalamus, are combined as a coherent and inseparable whole.

Within the theoretical framework of synchrony-mediated effective connectivity, von der Malsburg (1999) mused that “If there were mechanisms in the brain by which connections could directly excite or inhibit each other, fast retrieval of associatively stored connectivity patterns could be realized.” Implicitly, the BGMS model is a proposal that the BG, with the thalamus, implement such a mechanism, enabling patterns of activity in corticocortical connections to excite and inhibit other connections with nearly arbitrary flexibility. And as discussed later, similar mechanisms may be realized by other subcortical structures.
2. Precision Timing in Motor-Related Basal Ganglia Output

In this section:

2.1. The basal ganglia are integral to movement, but selective disinhibition is an inadequate model for their involvement.

2.2. Production of motor behavior implicates the basal ganglia at fine time scales.

2.3. Production of motor behavior entails long range oscillatory synchronies.

2.4. Production of motor behavior can be prevented by a single spike volley directed to a BG output structure.

2.1. The basal ganglia are integral to movement, but selective disinhibition is an inadequate model for their involvement.

It has long been recognized that the BG are integral to movement performance (DeLong and Georgopoulos, 2011; Chevalier and Deniau, 1990). Selective disinhibition of tonically inhibited motor centers, concurrent with enhanced inhibition of unselected motor centers, is a prominent model for this involvement (Chevalier and Deniau, 1990; Hikosaka et al., 2000). However, firing rate models do not fully describe the implicated mechanisms (Kojima et al., 2013). It is particularly telling that removal of ostensibly inhibitory pallidal input to thalamus for treatment of Parkinson’s disease (PD) does not result in an excess of movement (Brown and Eusebio, 2008; Marsden and Obeso, 1994), and that direct and indirect path activation have effects on activity levels in BG direct path output structures opposite those predicted by the inhibition-release model (Lee et al., 2016).

2.2. Production of motor behavior implicates the basal ganglia at fine time scales.

All cortical output to the brainstem and spinal cord arises from pyramidal neurons in L5, whose apical dendrites are in L1 (Deschénes et al., 1994), apposed directly by the terminals of BG-recipient thalamic projection neurons (Kuramoto et al., 2009; Jinnai et al., 1987). These appositions are excitatory. The apical and proximal dendritic processes of these pyramidal neurons are thought to interact as a coincidence detector (or “vertical associator”) mechanism, with a window width of 20-30 ms, particularly gating burst generation, with a significant correlation between the timing variability of the implicated thalamocortical spike activity and that of post-synaptic spikes (Larkum et al., 2004; Larkum, 2013). This implies that BG facilitation of thalamocortical spiking has temporal specificity at least as fine as this time scale. Somatic coincidence detection in pyramidal neurons is subject to a much tighter window, ~4 ms (Pouille and Scanziani, 2001; Volgushev et al., 1998), and evidence is reviewed later suggesting BG alignments at this much finer time scale, particularly implicating the intralaminar nuclei.

2.3. Production of motor behavior entails long range oscillatory synchronies.

Motor performance entails patterns of synchronized activity in motor neurons (Riehle et al., 1997; Hatsopoulos et al., 1998). In many neurons in premotor cortex, sustained oscillation at characteristic frequencies in high beta (typically 20-30 Hz) has been found to precede gestures, and to be selective for specific features of the forthcoming gesture (Lebedev and Wise, 2000). Granger causality analysis of LFPs in sensorimotor cortex suggests that sensory and inferior posterior parietal cortex drive sustained beta oscillation in motor cortex during a sustained gesture (maintenance of a hand press) (Brovelli et al., 2004). Oscillatory synchrony is apparent in premotor cortex during delay periods, and is displaced immediately before the onset of movement by simultaneous bursting (Lebedev and Wise, 2000).

Corticocortical gate control by the BG strongly implies oscillatory cortical activity. The delays of paths through the BG (e.g. 45 ± 15 ms via SNr to the frontal eye field, reviewed in detail later) are significantly longer than the corresponding corticocortical delays (e.g. 8-13 ms between area V4 in visual cortex and the frontal eye field (Gregoriou et al., 2009)), so that trans-BG spike volleys triggered by a given cortical spike volley return to cortex outside the coincidence window of that same cortical spike volley traveling corticocortically. Moreover, activation of the BG is dependent on synchronized cortical activity, due to physiology in the striatum (reviewed later). Thus, the BG can open a corticocortical gate, at the earliest, for the second in a series of synchronized spike volleys. Volleys from a particular efferent area must have a consistent cadence, even if only for a spike volley doublet, in order for coincident arrival to be possible (and, as proposed later, learnable) for volleys traveling both corticocortically and through the BG to the same target area. Of particular relevance to this mechanism, behavior-correlated spiking in premotor and primary motor cortex has been found to
always endure for at least one cycle of oscillation, and to often endure for only one (Churchland et al. 2012), representing the parsimonious spiking pattern for integration with the BG.

Sustained activity has also been proposed to be necessary for conscious cognition, entailing “dynamic mobilization” of long range functional networks (Dehaene and Naccache 2001; Dehaene and Changeux 2011). Irreducible delays in BG responses to preconscious cortical and thalamic activity may figure prominently in this dependency.

2.4. Production of motor behavior can be prevented by a single spike volley directed to a BG output structure.

That the BG generally facilitate effective connectivity using multi-areally synchronized spike volleys is suggested indirectly by the finding that a solitary, precisely timed spike volley from the subthalamic nucleus (STN) to the substantia nigra reticular part (SNr) can be effective in stopping (preventing) behavior (Schmidt et al. 2013). This might be evidence that the disruption of the timing of BG output is enough to abolish its facilitatory effect, so that its timing is implicitly critical. It also suggests that paths through the globus pallidus external segment (GPe) and the STN to the globus pallidus internal segment (GPi), SNr, and the reticular nucleus of the thalamus (TRN) may be temporally coherent, as proposed in the BGMS model for the direct path, and might induce calibrated antisynchronies to effect functional disconnections.

3. The General Nature of Basal Ganglia Direct Path Inputs and Outputs

In this section:

3.1. Basal ganglia outputs constitute decisions, and only incidentally relay information.
3.2. Basal ganglia output, and cortical activity patterns, are highly stochastic, implicating populations of neurons.
3.3. The basal ganglia preserve the temporal structure of afferent cortical activity.
3.4. GABAergic neurons can precisely control activity in their targets.
3.5. BG input to the thalamus is not purely inhibitory.

3.1. Basal ganglia outputs constitute decisions, and only incidentally relay information.

According to the BGMS model, the information represented by a pattern of activation in a particular cortical area passes to other receptive cortical areas chiefly via the direct connections between them. The information is not relayed through the BG, and reaches the thalamus via the BG in only drastically reduced and fragmentary form. While the striatum is continually supplied with inputs that apparently include nearly all cortically represented information (Parent and Hazrati 1995a; Hintiryan et al. 2016), only a small fraction of this information can emerge from the BG, due to the >1000:1 reduction in neuron count from the corticostriatal population to the output neuron populations in the GPi and SNr (Kincaid et al. 1998; Zheng and Wilson 2002; Goldberg and Bergman 2011). By a similar rationale, noting a 100:1 ratio of visual cortex neurons to pulvinar neurons in macaque, Van Essen (2005) suggested that the associative thalamus itself generally operates in a modulatory role, managing information transfers that are fundamentally corticocortical. This proposition is further supported by results, noted earlier, suggesting that the thalamic mediodorsal nucleus regulates functional connectivity in PFC rather than acting as an information relay (Schmitt et al. 2017).

3.2. Basal ganglia output, and cortical activity patterns, are highly stochastic, implicating populations of neurons.

Due to the general irregularity and independence of firing patterns in individual BG projection cells, the entropy of the BG paths is substantial (Wilson 2013). This suggests that decisions represented by BG output are highly flexible and can be quite nuanced. The neurons projecting from the BG to the thalamus are noted for their continuous and independent high frequency discharge patterns (Brown et al. 2001; Stanford 2002), and this activity must be functionally crucial, given its inherent metabolic burden, simultaneous with remarkable evolutionary stability, spanning hundreds of millions of years and all known vertebrate taxa (Stephenson-Jones et al. 2012). It has been suggested that these signals are particularly suited to act as carriers for motor commands (Brown et al. 2001); in the BGMS model these signals act as carriers for control signals spanning all domains.

Because each BG output neuron oscillates at an independent frequency, aggregate BG output statistically resembles Gaussian noise, suggesting that oscillatory modulation (by inputs from the striatum, in particular) can
produce output signals with high oscillatory fidelity. This is akin to dithering techniques that use additive noise with a triangular probability distribution to reduce harmonic distortion, in systems that represent intrinsically continuous signals using quantized digital schemes (Lipshitz et al. 1992). Convergence in mammals of several BG output neurons to single thalamocortical neurons (Ilinsky et al. 1997), and the multitude of thalamocortical neurons innervating each neighborhood in cortex (Rubio-Garrido et al. 2009), comport with such an arrangement. In the BGMS model, the resulting high temporal resolution lets the BG produce aggregate thalamocortical activity that is precisely coincident with converging corticocortical activity.

Moreover, there is evidence that oscillatory waveforms are often non-sinusoidal, conforming to various source-specific stereotypes (Cole and Voytek 2017). Functional significance has been ascribed to the fine time structure of spike “packets” exhibiting source-specific stereotypes over time spans of 50-200 ms (Luczak et al. 2015), and in general, to the information-carrying capacity of dynamic variations in inter-spike intervals (Tsien and Li 2017). To the degree that waveform harmonics and the fine time structure of spiking are functionally significant, waveform fidelity is likewise significant.

In cortex, individual neurons in a state of wakefulness exhibit almost completely random discharge patterns (Softky and Koch 1993). Computational modeling suggests that top-down synchronizing influences on a population of cortical neurons (of the sort exerted by thalamocortical projections, reviewed in detail later) profoundly impact their aggregate oscillation, evident in the LFP, with highly selective attentional effects, even while individual cells within the population continue to exhibit nearly Poissonian random firing patterns (Ardid et al. 2010).

In recent experiments with monkeys, it was found that movement-related LFP oscillations in GPi and its target area in thalamus (ventral lateral, anterior part, VLa) were strongly and likely causally correlated, for the duration of each trial, with a time lag from GPi to thalamus shorter than 10 ms, even while individual neuronal firing patterns in GPi showed little correlation to GPi LFP, and virtually no correlation to LFP in thalamus (Schwab 2016, chapter 5). The presence of movement-related LFP oscillation in GPi signifies phasically correlated discharges in large numbers of neurons there, whereas the weakness or absence of apparent spike synchrony signifies that the neurons discharging synchronously are sparsely embedded within a much larger number of neurons whose discharges are not correlated. While this is expected from the known physiology of the GPi, discussed above, and at greater length later, it is doubtless methodologically frustrating.

3.3. The basal ganglia preserve the temporal structure of afferent cortical activity.

A variety of evidence suggests that the BG process and preserve oscillatory time structure, positioning them to manipulate cortical synchronies. For some time it has been appreciated that cortico-BG circuits in a state of health show synchronized oscillations across the full spectrum of power bands, from the “ultra-slow” (0.05 Hz) to the “ultra-fast” (300 Hz), with robust oscillatory activity in the striatum and STN of alert behaving animals (primate and rodent) that is modulated by behavioral tasks (Boraud et al. 2005). In PD patients treated with levodopa, it has been observed that BG oscillation in the high gamma band appears to entrain cortex, with the BG leading cortex by 20 ms (Williams et al. 2002). In normal monkeys, task-related beta band oscillations in PFC follow and, according to Granger analysis, are caused by, activity in the striatum; this striatal activity, and that of its targets, sustain a spatially focused phase lock, with no inter-areal delay at beta (Antzoulatos and Miller 2014).

BG output responds quickly to sensory stimuli, accommodates and is sustained during delays, and precedes behavioral responses (Nambu et al. 1990). The striatum synchronizes with cortical theta (Berke et al. 2004) and gamma (Jenkinson et al. 2013) oscillation, and populations of neurons within each of the successive and parallel nuclei of the BG can synchronize with cortical beta oscillation, each nucleus exhibiting a task-related characteristic phase relationship with cortical oscillation that becomes consistent and precise with task mastery, and is most pronounced at the moment of task-critical decision (Leventhal et al. 2012). Moreover, as alluded to earlier, BG beta synchrony with cortical oscillation associated with a task-relevant sensory cue is established with an entraining phase reset that is sharp and immediate, within tens of milliseconds following presentation of an auditory stimulus (Leventhal et al. 2012).

3.4. GABAergic neurons can precisely control activity in their targets.

In cortex, GABAergic fast spiking inhibitory interneurons (FSIs) play a dominant role in the induction and control of oscillatory activity in the beta and gamma bands, exerting fine control over phase (Hasenstaub et al. 2005). Similarly in thalamus, GABAergic projections from the reticular nucleus are believed to be crucial to the induction of the intense, globally synchronized spike bursts known as sleep spindles (Contreras et al. 1997).

GABA, classically viewed as an inhibitory neurotransmitter, has a biphasic excitatory effect in certain circumstances, as a function both of the intensity of GABAergic release, and of the timing relationship between that release and the post-synaptic activity with
which it interacts; GABA activity can either inhibit or enhance NMDA-dependent synaptic plasticity as a function of that timing relationship (Staley et al. 1995; Lambert and Grover 1995). Consistent with these in vitro and in vivo results, computer simulation suggests that cortical FSIs can substantially raise the sensitivity or gain of their targets when interneuronal input and excitatory input are synchronized with an appropriate phase relationship (Tiesinga et al. 2004).

There is evidence of some of these effects, particularly biphasic activation and entrainment, in the GABAergic innervation of the thalamus by the BG (Goldberg et al. 2013; Bodor et al. 2008). These effects are particularly accessible to experimental probing in songbirds, where BG-recipient neurons in thalamus exhibit physiological similarity to mammalian thalamocortical cells, but unlike mammals, each receives only a single pallidal/nigral fiber, terminating in a calyx enveloping the soma (Luo and Perkel 1999). Studies in songbird thalamus have found coherent oscillatory entrainment at pallidothalamic terminals, and synchronous post-synaptic oscillation driven by pallidal input in the absence of excitatory presynaptic input (Person and Perkel 2005; Doupe et al. 2005; Leblois et al. 2009).

3.5. BG input to the thalamus is not purely inhibitory.

Simultaneous phasic intensification of ostensibly inhibitory pallidal output and activity in its thalamic targets has also been noted (Goldberg et al. 2013; Lee et al. 2016). This has several possible explanations, among which are the effects described above, and the actions of dopaminergic, cholinergic, and serotonergic nuclei, which facilitate responsive oscillation, and are integral to BG circuitry (these paths and effects are reviewed later). It may also be explained by coexpression of excitatory neurotransmitters in the pallidothalamic projection, or indeed within the terminal processes of individual axons therein, which could be particularly effective at entraining a target. Indeed, several studies have found a glutamatergic component within the pallidothalamic and nigrothalamic projections (Kha et al. 2000, 2001; Conte-Perales et al. 2011; Yamaguchi et al. 2013; Antal et al. 2014).

The tonic level of activity in BG-recipient thalamus is similar to that in cerebellum-recipient thalamus, even though the latter is subject to tonic excitatory input, and the two compartments show no apparent distinctions in cholinergic or TRN innervation (Nakamura et al. 2014). This apparent paradox may be explained not only by the effects described above, but by systematic cytological preferences, in which the BG and cerebellum target cytologically distinct thalamic populations, with distinct physiology and connectivity (Kuramoto et al. 2009; Jones 2001). However, it seems clear that much of the explanation is in the nature of the BG input itself, given findings noted earlier, that no excess of movement follows from PD treatments in which BG inputs to thalamus are removed (Brown and Eusebio 2008; Marsden and Obeso 1994).

Notably, just as thalamic activity increases simultaneous with increases in GPi activity, GPi metabolism and spiking activity increase simultaneous with activation of the direct path spiny projection neurons (SPNs) in the striatum that target it (Lee et al. 2016), despite similar ostensibly inhibitory chemistry in the striatopallidal projection. Moreover, physiologically realistic modeling suggests that striatal FSI activation, ostensibly inhibiting connected SPNs, increases the firing rates of those SPNs (Humphries et al. 2009). These are the relationships needed for oscillatory relay through the successive stages of the BG, and are incompatible with models in which BG actions are limited to inhibition and release.
4. The Cortical Origins and Targets of the Basal Ganglia Direct Path

In this section:

4.1. Direct path output is directed to most of the cerebral cortex, emphasizing frontal areas but including posterior areas.

4.2. The laminar hierarchical architecture of the cerebral cortex implies a role for the BG in orienting attention, biasing competition, and other roles associated with corticocortical feedback projections.

4.3. BG output in the normal brain is modulatory.

4.4. The BG target apical dendrites in cortex, through thalamic projections with mesoscopically and multi-areally branching axons.

4.5. Thalamocortical projections to apical dendrites control spike-timing-dependent gain.

4.6. Intrinsic mechanisms in cortex facilitate semantically valid mesoscopic modulation and selection.

4.7. Dopamine under BG control modulates the vertical and horizontal dynamics to which effective connections in cortex are subject.

4.8. Projections to thalamus from cortical layer 6 exhibit topography, and bear activity, suited to mesoscopic modulation by BG direct path output.

4.9. Intrinsic cortical network dynamics assure a supply of activity to thalamus that can be effectively entrained by converging BG inputs.

4.10. Motor and intralaminar thalamus relay BG-modulated cortical activity to BG inputs, with functional distinctions suggesting contextualization and dynamical regulation.

4.1. Direct path output is directed to most of the cerebral cortex, emphasizing frontal areas but including posterior areas.

In the BGMS model, it is through the direct path that cortical activity is focused, selected, and coherently distributed, establishing long range connections implicating the areas originating the selected activity. The circuitry and scope of the direct path are thus of paramount importance.

Direct path targets include the near entirety of frontal cortex, via thalamic mediodorsal (MD), ventral anterior (VA), ventral lateral (VL), ventromedial (VM), and ventral posterolateral pars oralis (VPLo) nuclei (Middleton and Strick 2002; Sidibé et al. 1997; Haber and Calzavara 2009; Sakai et al. 1996; Herkenham 1979). In primates, agranular insular and anterior cingulate cortex are targeted via MD (Ray and Price 1993), and additional targets include high-order visuocognitive areas in inferotemporal cortex via the magnocellular part of VA (VAmc) (Middleton and Strick 1996), and anterior intraparietal (Clower et al. 2005) cortex. These latter two areas are at the end of the ventral and dorsal visual streams, respectively, proposed to be associated with perceptual cognition relating to physical objects (Baizer et al. 1991), and have been found to show choice-predictive beta band synchronization in a 3D-shape discrimination task (Verhoef et al. 2011), plausibly implicating the BG directly (Leventhal et al. 2012). In chimpanzee, limited experiments have demonstrated projections from the MD, VA, and VL nuclei to posterior cortical areas 19 and 39 (Tigges et al. 1983). In humans, the dorsal and ventral visual streams in these areas are densely interconnected (Takemura et al. 2016), suggesting a role for BG-mediated inter-stream effective connectivity control in the middle stages of visual processing.

Extensive but diffuse projections from BG-recipient intralaminar nuclei (centromedian (CM), parafascicular (PF), paracentral (PC), and central lateral (CL)) have been found to reach nearly the entire cerebral cortex, and furthermore project intrathalamically and to the basal forebrain (Kaufman and Rosenquist 1985b; Scannell 1999; Van der Werf et al. 2002).

Consistent with these widespread projections of BG-recipient thalamus, artificial stimulation of direct path SPNs in the striatum significantly and consistently increases activity throughout the entire cortex (Lee et al. 2016).

4.2. The laminar hierarchical architecture of the cerebral cortex implies a role for the BG in orienting attention, biasing competition, and other roles associated with corticocortical feedback projections.

The laminar function of cortex, and the layer-specific targeting of corticocortical projections, can help explain the functional relationship of the BG to cortex. An arrangement of cortical areas in primates has been described in which hierarchies are defined by long range
feedforward and feedback relations, with characteristic laminar origins and destinations that grow more distinct as hierarchical distance grows (Barone et al. 2000). In primates, feedforward projections tend to arise from L5 and deep L3, adjacent to L4 (the middle granular layer), and project to L4, while feedback projections arise from L6 and upper L3, and project to L1/L2, upper L3, and L6 (Barone et al. 2000; Markov and Kennedy 2013). The functions ascribed to feedback projections include attentional orientation by biasing competition, and disambiguation and hypothesis-driven interpretation of high resolution feedback inputs (“biasing inference”), while feedforward projections introduce environmental state information into hypothetical representations (models), promoting rectification of their inaccuracies and inadequacies (Markov and Kennedy 2013).

Cortical inputs to striatal matrix, including the direct and indirect paths, arise from L3 and L5 (Gerfen 1989; Kincaid and Wilson 1996; Reiner et al. 2003), like corticocortical feedforward paths. This suggests that the BG receive detailed, highly specific, environmentally informative inputs. However, BG-recipient thalamocortical axons terminate chiefly in L1, L3, deep L5, and L6, and completely avoid L4 (Kuramoto et al. 2009; Jinmai et al. 1987; Parent and Parent 2005; Kaufman and Rosenquist 1985a; Berendse and Groenewegen 1991). Thus, the termination pattern of BG-recipient thalamus in cortex is like that of corticocortical feedback paths, consistent with the putative role of the BG as a modulator and selection mechanism, and suggests a key role in hypothetical modeling of the environment. In L5, a particular need for disambiguating inputs is suggested by evidence that neurons responsive to varied stimuli are prevalent in L5, while narrower receptive fields, providing for nearly comprehensive combinatorial coverage of stimulus dimensions, predominate in L2/L3 (Xie et al. 2016; Li et al. 2016).

The cortical input to BG-recipient thalamus arises both from L6, and from collaterals of command output to the brainstem and spinal cord arising from L5 (Deschénes et al. 1994), pooling afferents whose origins resemble those of corticocortical feedback and feedforward projections. This might have consequences for interactions with BG output, discussed later. Also discussed later, projections from the thalamus back to striatum relay this pooled input, which intermingles convergently with the more plentiful cortical inputs.

Some projections of the PFC to posterior areas have been found to resemble those of the BG-recipient thalamus, terminating most densely in L1 and avoiding L4, in the pattern of feedback projections (Selemon and Goldman-Rakic 1988). Transthalamic paths from cortex through “core” neurons in the thalamus, on the other hand, have been found to originate chiefly in L5, and to terminate in L4 and deep L3 (Jones 2001; Rouiller and Welker 2000), like corticocortical feedforward paths. Similarly, input to the cerebellum from the neocortex arises from deep L5 (Glickstein et al. 1985; Schmahmann and Pandya 1997), and its output targets the core population in thalamus and, through them, middle layers in cortex (Kuramoto et al. 2009; Garcia-Cabezas and Barbas 2014), so that many paths through the cerebellum also resemble corticocortical feedforward paths.

### 4.3. BG output in the normal brain is modulatory.

Movement is difficult or impossible to evoke by electrical stimulation of BG-recipient loci in the motor thalamus, even while such movement can be readily evoked from nearby loci receiving cerebellar output (Vitek et al. 1996; Buford et al. 1996; Nambu 2008). As noted above, cerebellum-recipient cells project mainly to middle cortical layers, while BG-recipient cells project mainly to deep and superficial layers. In primate, BG-recipient neurons in the motor thalamus may be consistently within the calbindin-positive population, associated with widely distributed and divergent cortical modulation, while cerebellum-recipient neurons are consistently within the parvalbumin-positive population, associated with specific and narrowly circumscribed topographic projections (Jones 2001; Kuramoto et al. 2009).

While movement can be evoked by microstimulation of the intralaminar nuclei (Schlag et al. 1974), BG input there, as in the nigrotectal projection, is mostly directed to the dendrites of projection neurons (Sidibé et al. 2002; Behan et al. 1987), where it can only modulate other, excitatory inputs. This contrasts with calyx-like BG terminals in the motor thalamus, that exercise predominant control over their targets, and can directly induce rebound firing and bursting (Bodor et al. 2008).

### 4.4. The BG target apical dendrites in cortex, through thalamic projections with mesoscopically and multi-areally branching axons.

Outside the intralaminar nuclei, projections of the BG-recipient thalamus terminate chiefly in L1 (the molecular layer, consisting mostly of the apical dendrites of pyramidal neurons), while projections of cerebellum-recipient thalamus terminate chiefly within L2-L5; the two terminal fields overlap and intermingle in cortex so that pyramidal neurons are simultaneously under the influence of the BG and cerebellum (Kuramoto et al. 2009; Jinmai et al. 1987). The rat and cat VM nucleus, a major recipient of SNr output, has been noted for directing its output, covering large portions of the cerebral cortex, almost exclusively to L1 (Herkenham 1979; Glenn et al. 1982). Recent experiments in the rat have demonstrated that thalamic projections to superficial cortex are comprehensive, extensively overlapping, broadly arborize tangentially, and are variously intra- and inter-areally divergent and convergent (Rubio-Garrido et al. 2009).
Each square mm of superficial cortex was found to be innervated by an average of ~4500 thalamocortical neurons, and the most profuse nuclei of origin were the VL, VA, and VM, each of which was noted for terminal fields targeting widely separated areas in cortex. Primary sensory nuclei were found to be completely absent from the projection to superficial cortex.

Broadly branching axons, and the absence of contributions by primary sensory thalamus, suggest a mesoscopic modulatory function for these projections. In vitro experiments in rat suggest that apical inputs to L5 neurons have a negligible direct effect on the soma, due to severe attenuation, and shunting by back-propagating action potentials (Larkum et al. 2004). Moreover, beta (and higher) oscillation in the BG, reaching superficial cortex, apparently does not in itself manifest as oscillation at the somata of receiving cortical projection neurons, but rather appears to be low-pass filtered with a cutoff frequency of 5 Hz (Rivlin-Etzion et al. 2008).

4.5. Thalamocortical projections to apical dendrites control spike-timing-dependent gain.

When thalamocortical projections provide subthreshold input to the L1 apical dendrites of L5 pyramidal neurons, that input appears to selectively increase the effective gain of the pyramidal neurons, such that temporally coincident input (within 20-30 ms) to their somata induces bursting output (Larkum et al. 2004). According to the BGMS model, BG-influenced activity in these thalamocortical projections, exhibiting multi-areal synchrony, reinforces activity in selected cortical areas, both those that triggered the BG response, and associated areas that are contextually relevant. If corticocortical bursting itself effects long range synchronization (Womelsdorf et al. 2014), then the BG may instantiate long range synchronies by controlling and coordinating the location and timing of cortical bursting and burst receptivity. Paths through the intralaminar nuclei to deep cortical layers are likely critical to the temporal coordination and selectivity of these responses, as discussed in detail later.

4.6. Intrinsic mechanisms in cortex facilitate semantically valid mesoscopic modulation and selection.

The density and overlap of the thalamocortical projection to L1 (Rubio-Garrido et al. 2009) suggest that BG output associated with consolidated skills recruits comprehensive modulation of targeted cortical areas. Beyond the domain of well-worn skills, there are intrinsic mechanisms in cortex that may heal intra-areal gaps in modulation. It has been proposed that activity entering cortex through L1 spreads horizontally through L2 and L3, yielding mesoscopic facilitation of firing in L5 pyramidal cells, thereby controlling long range effective connectivity (Roland 2002). Lag-free lateral spread of oscillation up to high gamma has been demonstrated in vitro, working through interactions in L2 and L3, entailing an ensemble dynamic of gap junctions and GABAergic fast spiking interneurons (Tamás et al. 2000).

The neurons of L2 (the external granular layer) have larger receptive fields and a higher incidence of combined feature selectivity than neurons of lower layers, and their projections are exclusively corticocortical (Markov and Kennedy 2013). The apical dendrites of the small pyramidal neurons of L2 intermingle in L1 with the apical dendrites of L5 pyramidal neurons, spreading 100-200 µm laterally (Meller et al. 1968; Noback and Purpura 1961). Because these layers are adjacent, the implicated thalamocortical appositions are more proximal, so likely subject to markedly less of the attenuation and filtration characterizing apical inputs to L5 neurons. Putative high frequency BG modulation of thalamocortical projections to L1 might therefore induce correlated discharges in L2 pyramidal neurons, spreading this high frequency activity laterally within the superficial layers. Moreover, in vitro experiments with pyramidal neurons from these layers have demonstrated nonlinear coincidence detection dynamics, with windows only 4-7 ms wide (Volgushev et al. 1998), suggesting temporal specificity in L2/L3 mechanisms sufficient to bias competition among conflicting gamma oscillations.

Discontinuities have been found in the local horizontal linkages of cortex, particularly in L2 and L3, that are posited to tessellate sensory areas along boundaries of similar function and features (Rockland and Lund 1983; Ojima et al. 1991; DeFelipe et al. 1986; Juliano et al. 1990). Similar tessellation, into “stripes” 2-3 mm long and 200-400 µm wide, has been described in PFC (Levitt et al. 1993; Pucak et al. 1996), and is posited to define the limiting spatial resolution with which the BG can modulate cortical activity (Frank et al. 2001). Spreading, but spatially restricted, synchronized activation of superficial modulatory layers has semantically valid effects with a cortical layout in which mental categories and analogs are represented by precise, spatially graded semantic continuities—feature maps—not only in sensory receptive fields, but throughout the cerebral cortex, as evidence suggests (Rao et al. 1999; Huth et al. 2012; Simmons and Barsalou 2003).

4.7. Dopamine under BG control modulates the vertical and horizontal dynamics to which effective connections in cortex are subject.

Striosomal BG paths (reviewed later) are major modulators of the supply of dopamine (DA) to the forebrain. While DA promotes oscillatory responses to activity in proximally apposed afferents to pyramidal neurons, it has been found to attenuate receptivity to inputs on apical dendrites, which may “focus” or “sharpen” the effects of inputs to those cells (Yang and Seamans 1996).
Moreover, the GABAergic interactions among L2/L3 basket FSIs that are crucial for the elimination of phase lags in laterally spreading oscillation (Tamás et al. 2000) are depressed by DA (Towers and Hestrin 2008). This suggests that phasic DA induces phase lags in L2/L3 that increase with distance from the locus of excitatory input, perhaps producing a center-surround effect that effectively focuses cortical responses. Because expressions of plasticity are pervasively spike-timing-dependent (Song et al. 2000), this phase lag control mechanism may also have important consequences for the formation and refinement of cortical feature maps.

These arrangements suggest a corollary to the central proposition of the BGMS model: not only do the BG control effective connectivity in cortex, they also separately control the dynamic characteristics of effective connections. BG influences on cholinergic and serotonergic centers, reviewed later, extend this control.

4.8. Projections to thalamus from cortical layer 6 exhibit topography, and bear activity, suited to mesoscopic modulation by BG direct path output.

Most of the corticothalamic population arises from L6, with small terminals apposing distal dendrites in thalamus, and reciprocation is particularly prominent in this projection (Rouiller and Welker 2000). The corticothalamic projection topographically and comprehensively reciprocates the thalamocortical projection, with consistent rules such that each thalamic locus that originates a given type of projection to cortex has a corresponding corticothalamic type reciprocated (Deschênes et al. 1998). It has been demonstrated in somatosensory areas that projection cells in upper L6 narrowly reciprocate with their functional counterparts in thalamus, while the terminal fields of some, perhaps all, lower L6 projection cells spread laterally to reciprocate both their afferent locus and that locus’s neighbors in thalamus (Rouiller and Welker 2000). As reviewed above, the associated thalamocortical axons extensively branch intracortically in superficial cortex.

In an in vitro study in rat, the delay of the corticothalamic projection from L6, and its variability, were found to be significantly greater than those of the thalamocortical projection, 5.2 ± 1.0 ms and 2.1 ± 0.55 ms respectively (Beierlein and Connors 2002). While thalamocortical delays are essentially fixed and very tightly aligned (Salami et al. 2003), L6 corticothalamic delays evidence supernormality. This entails reduction of delay and threshold below baseline after the relative refractory period (Swadlow et al. 1980). Supernormality was found to persist for roughly 100 ms following a discharge, and with a 40 Hz stimulus it reduced corticothalamic delay by up to 12% (Beierlein and Connors 2002). While the functional significance of supernormality in the corticothalamic projection is elusive, it might arrange for advancement of spike timing in cortex as activity intensifies, either matching supernormality in implicated corticocortical projections, or producing other useful timing-related effects, such as phase-of-firing intensity encoding (Masquelier et al. 2009).

The numerosity, structure, and variability of the L6 corticothalamic projection suggest it may be subject to some of the same pressures producing convergence, divergence, and variability in the corticostriatial and striatopallidal projections—particularly, the need for a supply of inputs with appropriate characteristics to meet complex and widely varying topological and spike alignment requirements in paths through thalamus terminating in feedback-recipient layers of cortex. These arrangements are discussed at much greater length later.

4.9. Intrinsic cortical network dynamics assure a supply of activity to thalamus that can be effectively entrained by converging BG inputs.

A full account of the function of the corticothalamic projection has proved elusive (Goldberg et al. 2013). According to the BGMS model, the corticothalamic projections from L5 and L6 to BG-recipient thalamus arrange for BG output to be able to select, in each channel, which frequency and phase of cortical activity is to be reinforced and which are to be inhibited. Evidence and modeling suggest that conflicting rhythms in the afferent activity to a cortical neuron shift their discharge patterns away from rhythmic regularity and toward randomness (Gómez-Laberge et al. 2016). Such a response might work to assure that corticothalamic afferents from conflicted cortical loci, converging with BG afferents, can produce postsynaptic activity entrained by those BG afferents, for any particular frequency and phase of BG-selected activity. Moreover, the population of corticothalamic fibers is considerably more numerous than the thalamocortical population, by roughly a factor of 10 (Deschênes et al. 1998), and as noted above, pools afferents from L5 and L6. This suggests a relatively high degree of convergence in the corticothalamic projection, further working to assure a supply of suitable excitatory afferent activity, and including activity associated with both feedforward and feedback projections.

4.10. Motor and intralaminar thalamus relay BG-modulated cortical activity to BG inputs, with functional distinctions suggesting contextualization and dynamical regulation.

While the main input to the matrix compartment of striatum arises from L3 and L5, as reviewed above, there are profuse projections from BG-recipient thalamus to striatum, implicitly relaying input from L6. Inputs from cortex and thalamus converge on individual SPNs, with similar axodendritic patterns, but with cortical inputs more...
The intralaminar nuclei are a uniquely important link between the basal ganglia and cerebral cortex.

Compared to the motor and association nuclei, the intralaminar nuclei of the thalamus are small, but they have exceptional characteristics and functions placing them at the very center of cognitive coordination and awareness. Moreover, among thalamic nuclei, the intralaminars are uniquely intimate with the BG, and indeed have been described as an integral part of the BG system (Parent and Parent 2005). In the BGMS model, the intralaminar nuclei, through their broad projections and numerous (Huerta-Ocampo et al. 2014). Projections from thalamic VA/VL to striatum converge with functionally corresponding projections from cortex (McFarland and Haber 2000). Evidence from primates shows that striatal FSIs are likely broadly targeted by projections from intralaminar thalamus (Sidibé and Smith 1999). Intralaminar projections have also been noted for supplying the striatum with information relating to salient sensory events (Matsumoto et al. 2001), and are implicated in the learning of changes in instrumental contingencies, through projections to cholinergic interneurons (Bradfield et al. 2013). In vitro experiments demonstrate projections from the thalamus to striatal SPNs, with distinctive synaptic properties, such that postsynaptic response generation is likelier than for corticostriatal synapses, but repetitive stimulation depresses postsynaptic depolarization (Ding et al. 2008). In awake monkeys, activation of projections from intralaminar thalamus to striatum has complex effects, with SPN discharge induced only by rapid bursts from thalamus, and long latencies peaking 100-200 ms after intralaminar stimulation (Nanda et al. 2009).

Significantly, intralaminar thalamostriatal projections strongly prefer the matrix compartment (Sadikot et al. 1992b) to which the direct and indirect paths are confined. Thalamostriatal and thalamocortical projection neurons in the intralaminar nuclei are intermingled, and many axons branch to innervate both striatum and cortex (Deschênes et al. 1996; Parent and Parent 2005; Kaufman and Rosenquist 1985a), so that synchronies in the striatal projections of these nuclei are presumptively representative of synchronies in their cortical projections. Thus, thalamostriatal inputs implicitly reflect the current effect of BG output upon the cortex. These subcortical feedback loops may facilitate regulation of BG output to bring modulatory results into conformity with intentions, both dynamically and, as discussed later, by driving the expression of plasticity.

They may also provide for sequential elaboration of BG output, adjusting thalamocortical modulations with greater speed and precision than is possible within cortico-BG loops. Intralaminar thalamic projections to the globus pallidus, substantia nigra, and subthalamic nucleus (Sadikot et al. 1992a) may serve similar roles, exploiting loop delays that are much shorter than the propagation delays of the corticostriatal and striatopallidal projections (Kitano et al. 1998; Haruno and Filion 1982). Moreover, tight integration of the BG with the cerebellum through subcortical pathways has been noted (Bostan and Strick 2010; Bostan et al. 2013), and seems likely to be prominent in mechanisms underlying performance of rapid, precise, sequential cognition and behavior.

In this section:

5.1. The intralaminar nuclei are a uniquely important link between the basal ganglia and cerebral cortex.
5.2. Intralaminar thalamus in primates projects to pyramidal somatic layers.
5.3. The thalamocortical projections of the BG-recipient intralaminar nuclei reach nearly the entire cortex.
5.4. Unlike other BG-recipient thalamic areas, the intralaminar nuclei of the thalamus are not purely modulatory.
5.5. The characteristics of the BG-recipient intralaminar nuclei suggest high fidelity relay of precisely timed activity.
5.6. Most BG output to the intralaminar nuclei is non-somatic, increasing combinatorial power and decoupling BG output from cortical somatic inputs.
5.7. Cortical projections to CM/PF predominantly arise in layer 5, as do many corticocortical projections.
5.8. Intralaminar and non-intralaminar projections from BG-recipient thalamus have complementary functions.
5.9. The BG-recipient intralaminar nuclei are most developed in humans.
5.10. The BG-recipient intralaminar nuclei may be critical to the expression of pathology in Tourette syndrome, OCD, and schizophrenia.
5.11. Disruption in schizophrenia of sleep spindling and prefrontal FSI activity likely grossly disrupt BGMS.
5.12. Reports on the functional correlations of the intralaminar nuclei, and their physiological relationships with the basal ganglia and cortex, likely supply some of the best available evidence supporting the BGMS model.
dynamical characteristics, work as a high fidelity broadcast mechanism whereby long range effective connectivity, and therefore cognition, are oriented by spike-timing-dependent gain.

5.2. Intralaminar thalamus in primates projects to pyramidal somatic layers.

Some studies in rat and cat report intralaminar thalamocortical projections principally targeting L1 (Royce and Mourey 1985; Royce et al. 1989), like the projections of the BG-recipient populations in the MD, VA, VL, VM, and VpLo nuclei, whereas other studies in primate, rat, and cat report intralaminar projections principally to L5 and L6, where individual axons branch widely and arborize massively to appose the somata and proximal dendrites of great numbers of pyramidal neurons, and may terminate in L1 only more sparingly (Parent and Parent 2005; Kaufman and Rosenquist 1985a; Berendse and Groenewegen 1991; Linas et al. 2002). The disparities among these studies have been suggested to relate to actual physiological distinctions among the species at issue, made all the more likely by the particularly active recent evolutionary history of the intralaminar nuclei and cerebral cortex (Royce and Mourey 1985), but may simply be methodological artifacts.

5.3. The thalamocortical projections of the BG-recipient intralaminar nuclei reach nearly the entire cortex.

While intralaminar projection fibers to frontal cortex are greatly outnumbered by those from non-intralaminar BG-recipient thalamic nuclei (Barbas et al. 1991; Schell and Strick 1984), intralaminar projections are strikingly widespread, encompassing nearly the entire neocortex. Experiments in rats and cats demonstrate that the CM/PF nuclei, comprising the caudal group, project to motor, frontal eye fields (FEF), orbitalfrontal, anterior limbic, cingulate, parietal, and visual cortex, and to many structures of the medial temporal lobe, though not to the hippocampus proper (Royce and Mourey 1985; Berendse and Groenewegen 1991). In the same two species, the rostral CL and PC nuclei project widely but without consistent topography to the FEF, anterior cingulate, insular, parietal areas 5 and 7, visual excluding only area 17, and auditory cortex (Kaufman and Rosenquist 1985a; Royce et al. 1989; Berendse and Groenewegen 1991). Single axons from CL and PC have been noted to branch multi-areally to innervate visual and parietal association cortex, suggesting a general function for the intralaminar nuclei, rather than specific functions in the spatial processing of visual information (Kaufman and Rosenquist 1985a). A metastudy pooling thalamocortical and corticothalamic projections in cat concluded that the intralaminar nuclei connect very widely with most of visual, auditory, motor, and prefrontal cortex; though nearly all of these connections were characterized as weak or sparse, of 53 cortical areas studied, only 7 (the contiguous primary, posterior, ventroposterior, and temporal auditory fields, the posterior suprasylvian area of visual cortex, and the hippocampus/subiculum) were not reported to be connected with any of the BG-recipient intralaminar nuclei (Scannell 1999).

The broad cortical projection field of the intralaminar nuclei, their extreme divergence, and their intimacy with oscillatory dynamics, were demonstrated by the “recruiting response” reported in early experiments in cats. Oscillatory activity spanning nearly the entire cerebral cortex, most strongly in frontal areas, was evoked with electrical stimulation centered anywhere within the intralaminar region (Morison and Dempsey 1941; Dempsey and Morison 1941). The ventral anterior and mediodorsal nuclei, prominent in the system of superficially projecting BG-recipient thalamus detailed earlier, exhibit similar indications of large scale connectivity. The ventral anterior nucleus in particular has also been implicated in the generation of the recruiting response (Skinner and Lindsey 1967).

CNS insults that bilaterally destroy not only the rostrocaudal extent of the intralaminar nuclei, but also the adjacent MD nucleus, are consistently associated with the permanent vegetative state (Schiff 2010). Pharmacological manipulation of the intralaminar nuclei can rapidly abolish or restore wakefulness (Alkire et al. 2008), and a special indispensability to consciousness has been proposed for these nuclei (Bogen 1995; Baars 1995).

Sleep spindles, which entail tightly synchronized responses spanning large areas of cortex, also demonstrate the broad scope of intralaminar projections. In spindling, activity in the corticothalamic projection and thalamic reticular nucleus are thought to drive thalamocortical cells to simultaneous discharge in nuclei spanning much of the thalamus, particularly through highly divergent projections from the rostral reticular nucleus through the BG-recipient intralaminar and association nuclei (Contreras et al. 1997).

5.4. Unlike other BG-recipient thalamic areas, the intralaminar nuclei of the thalamus are not purely modulatory.

The CL and PC nuclei in cats contain neurons whose activity is uniquely related to all kinds of eye movements, fast or slow, self-initiated or evoked, to stimuli and movements characterized visuotopically, allocentrically, by direction of gaze, and various combinations thereof, to eye position, and to polysensory context and vigilance (Schlag et al. 1974, 1980). Activity in these neurons precedes saccade onset by 50-400 ms, and continues during the saccade, whether the saccade is self-initiated or visually evoked, with each neuron showing a consistent but idiosyncratic pattern (Schlag et al. 1974; Schlag-Rey...
coincidence detectors with windows only 4-7 ms wide, that become narrower with rising oscillatory frequency, with the timing of discharges tightly correlated to the timing of somatic membrane potential oscillation (Volgushev et al. 1998).

5.6. Most BG output to the intralaminar nuclei is non-somatic, increasing combinatorial power and decoupling BG output from cortical somatic inputs.

As noted above, BG inputs to primate caudal intralaminar thalamus overwhelmingly appose dendrites, not somata (Sidibé et al. 2002). These appositions are not homogeneous, in that over 80% of SNr inputs to PF in monkey were found to appose small or medium, mostly distal, dendrites, with none apposing somata, while over 75% of GPi inputs to CM were found to appose medium or large, mostly proximal, dendrites, and 5% to appose somata. These patterns of apposition clearly result in looser coupling between the BG and intralaminar thalamus than does the perisomatic, calyceal pattern seen in non-intralaminar BG-recipient thalamus (Bodor et al. 2008). Perhaps more important, by apposing the dendritic arbors of intralaminar projection cells, extensive nonlinear computation can be performed presomatically, enormously enhancing combinatorial flexibility. By this arrangement, a single intralaminar neuron might participate in a vast variety of scenarios characterized by distinct corticothalamic and nigrothalamic input patterns, each producing somatic discharges, but by different combinations of dendritic inputs.

5.7. Cortical projections to CM/PF predominantly arise in layer 5, as do many corticocortical projections.

While inputs from L6 predominate in BG-recipient motor/association thalamus, in BG-recipient caudal intralaminar thalamus it is L5 inputs that predominate (Van der Werf et al. 2002; Balercia et al. 1996; Cornwall and Phillipson 1988; Royce 1983a, 1983b). This mirrors targeting of L5 in thalamocortical projections from this area, discussed above, and moreover shares its laminar origin with many corticocortical projections (Reiner et al. 2003). This is significant, because it suggests that corticocortical projections are systematically accompanied by trans-intralaminar paths, sharing exactly the same origins and targets, and subject to temporally precise gating by the BG direct path, in which L5 is similarly predominant in inputs to striatum, as reviewed earlier.

5.8. Intralaminar and non-intralaminar projections from BG-recipient thalamus have complementary functions.

Widespread intralaminar projections appear arranged to broadcast a temporally precise but spatially diffuse signal

and Schlag 1977; Schlag et al. 1980). While each completed saccade is accompanied by a consistent pattern of activation in some of these neurons, the reverse is not always the case—the same pattern of activation in an intralaminar neuron is sometimes seen in the absence of an executed saccade (Schlag et al. 1974). Nonetheless, microstimulation in the CL and PC nuclei consistently evokes conjugate saccades with a delay of 35 ms for large deviations, suggesting primary involvement in saccade generation (Maldonado et al. 1980).

5.5. The characteristics of the BG-recipient intralaminar nuclei suggest high fidelity relay of precisely timed activity.

Unlike other BG-recipient populations in thalamus, the CM and PF nuclei are densely parvalbumin-positive (Jones and Hendry 1989). In other thalamic nuclei, as noted earlier, parvalbumin is associated with putative “core” or “driving” neurons, which are not BG-recipient, and in other brain organs, notably the cerebral cortex, striatum, GP, and SNr, parvalbumin is associated with fast-firing, fatigue-resistant neurons. Via the caudal intralaminar nuclei, the BG complete loops within which spike timing is largely determined by parvalbumin-containing, fast-firing, non-fatiguing neurons (Mallet et al. 2005; Bennett and Bolam 1994; Cote et al. 1991), targeting proximal dendrites and somata of pyramidal neurons in deep cortex as described above.

The rostral intralaminar nuclei are densely calbindin-positive (Jones and Hendry 1989), like non-intralaminar BG-recipient thalamus, but the CL nucleus contains a population of neurons that, during wakefulness and REM sleep, have been found to regularly emit bursts of 3-4 spikes with interspike intervals (ISIs) shorter than 1.3 ms, at a burst rate of 20-40 Hz, with no apparent signs of fatigue (Steriade et al. 1993). Bursts in these cells were found to be even more intense, 8-9 spikes with ISIs as low as 1 ms, in the spindling characteristic of stage 2 sleep.

Because BG inputs to intralaminar nuclei are collaterals of inputs to other thalamic nuclei (Parent et al. 2001), the information received from the BG by the intralaminar nuclei presumably duplicates that received by non-intralaminar cells. But high fidelity relay by neurons of the intralaminar thalamus, combined with pyramidal somatic layer targeting, appears to arrange for particularly narrow selectivity through spike synchrony effects. Indeed, a mechanism in cortex implicating fast-spiking interneurons arranges for an extremely narrow coincidence detection window for proximally apposed afferents to pyramidal neurons, -1.5 to +2.4 ms for effective spike summation, even while the coincidence requirement in distal inputs was found to be much looser, -8.6 to +12.3 ms (Pouille and Scanziani 2001). Even absent the influence of FSIs, pyramidal neurons stimulated somatically in vitro have been shown to act as nonlinear
to most of cortex, while non-intralaminar projections to superficial layers have mesoscopic spatial specificity, relatively crude temporal specificity, and more restricted areal targets. At the heart of the BGMS model is the proposition that the BG coherently modulate these two influences, so that their convergence and inter-areal linkage in cortex provide for spatiotemporal specificity and consequent precision in the control of effective connectivity. By interacting with intrinsic cortical activity, these inputs rapidly and dynamically recruit specific large scale networks.

The BGMS proposal can be summarized as follows: When an input pattern triggers a selection in the striatum, the timing of striatal output tracks the prevailing timing of the input pattern, and the GPi, VP, and SNr impart that timing to the thalamus, with striatopallidal and striatonigral delays tuned for optimum effect (optimality being a function of cortical rhythms and corticocortical conduction delays, discussed in detail later). The intralaminar nuclei, through widespread diffuse projections to L1 and L5, impart discriminative receptivity to any activity that is precisely synchronous with that prevailing in the input pattern that stimulated the BG response, and narrowly reinforce it in its loci of origin. The non-intralaminar nuclei, through dense, mesoscopically specific, largely closed-loop projections, chiefly to L1, fortify activity in selected areas, particularly those contributing to the input pattern. When this fortification is strong, and coincident with substantial activity in the corresponding proximally apposed afferents, bursting is promoted (Larkum et al. 2004), which may further promote establishment of effective connections (Womelsdorf et al. 2014).

Closed-loop paths through non-intralaminar nuclei largely implicate areas in frontal cortex, which are the densest targets of non-intralaminar BG-recipient thalamocortical projections, but other association areas in primates, notably in parietal and temporal cortex, are also implicated. All of these areas are thought to originate feedback signals with top-down control over their targets. By this narrative, the BG direct path establishes and fortifies top-down control connections from both ends, with the MD, VA, and VL nuclei fortifying the top end of the connection, and the CM, PF, PC, and CL nuclei tuning both ends to complete the connections.

Open loop direct paths through non-intralaminar nuclei may serve to complete activation of a distributed cortical ensemble that is only partly activated when it first triggers a striatal response, particularly when the triggering pattern largely originates in sensory cortex. Closed loop paths through intralaminar nuclei may tighten synchrony throughout the selected ensemble, and provide reinforcement that is highly selective, due to the narrow coincidence windows associated with proximal inputs to pyramidal neurons.

Notably, trans-intralaminar inputs may actively inhibit and disconnect activity that is not synchronous (particularly, that is antisynchronous) with the intralaminar signal, by feedforward inhibition via cortical FSIs. Indeed, the relative effect of intralaminar projections on pyramidal neurons and on their associated cortical FSIs is an important open question. It is clear from the response to sleep spindles (Peyrache et al. 2011) that both are targeted by thalamocortical projections, and feedforward inhibition associated with this arrangement enforces extremely short windows of summational receptivity (Pouille and Scanziani 2001).

It may be important that intralaminar projections, which target most of the cortex, are subject to extremely narrow coincidence windows. With wider windows, the intralaminar broadcast mechanism seems prone to establishment of spurious connections. Indeed, Sz involves abnormal enlargement of these coincidence windows (Lewis et al. 2005; Gonzalez-Burgos et al. 2015), while lesioning and deactivation of intralaminar nuclei has been found to relieve hallucinations and delusions associated with Sz and other psychoses (Hassler 1982). Sz is also characterized by enlargement of the time window within which visual stimuli are judged to be simultaneous (Schmidt et al. 2011), and by abnormalities in the simultaneity criteria for implicit audiovisual fusion (Martin et al. 2013). Beyond Sz, loosening of simultaneity criteria, and deficient perception of short time intervals, may be characteristic of psychosis generally (Schmidt et al. 2011; Ciullo et al. 2016).

5.9. The BG-recipient intralaminar nuclei are most developed in humans.

As evident from their function in vision and saccades, the BG-recipient intralaminar nuclei are a jumble of perceptual and motoric function, with activity in individual neurons highly correlated with both. Roles for these nuclei in executive control, working memory, and general cognitive flexibility—capacities that are most developed in humans—have also been shown (Van der Werf et al. 2002). Over the course of mammalian evolution, the intralaminar nuclei, particularly the posterior group, have undergone relative expansion and elaboration, reaching their greatest extent in primates, and in humans particularly (Macchi and Bentivoglio 1986; Royce and Mourey 1985; Herkenham 1986).

5.10. The BG-recipient intralaminar nuclei may be critical to the expression of pathology in Tourette syndrome, OCD, and schizophrenia.

Psychosurgical results in humans give further evidence that these nuclei can originate driving inputs to motoric, perceptual, cognitive, and motivational centers. Treatment of Gilles de la Tourette syndrome (GTS) by stereotactic
ablation or rhythmic electrical stimulation of the rostral (Rickards et al. 2008) or caudal (Houeto et al. 2005; Servello et al. 2008) intralaminar nuclei has produced substantial and sustained abatement, in some cases almost complete remission, of compulsive behavior (tics) in many patients. Similarly, severe or extreme symptoms of obsessive compulsive disorder (OCD) have been substantially, consistently, and sustainably alleviated by unilateral lesioning of the right intralaminar nuclei (Hassler 1982), or by rhythmic electrical stimulation localized to the inferior thalamic peduncle, inactivating connectivity between intralaminar nuclei and orbitofrontal cortex (Jiménez-Ponce et al. 2009). GTS and OCD involve extensive BG abnormalities (Graybiel and Rauch 2000; Albin and Mink 2006; Kalanithi et al. 2005), so alleviation of symptoms by IL inactivation suggests functional prominence of the intralaminar nuclei in BG dynamics, and may be evidence of key involvement in the transmission of BG output to cortex.

Functional deficits in Sz are intimately related to the functional roles of the intralaminar nuclei. Eye tracking and saccade control are dysfunctional, suggesting particular deficits in anticipatory control and the suppression of distractors (Levy et al. 1994; Fukushima et al. 1988; Hutton et al. 2002), and aberrant connectivity between the intralaminar nuclei and PFC has also been described (Lambe et al. 2006). Sz has been found to be associated with significant relative reduction in volume and metabolic hypofunction specific to the centromedian nucleus, in addition to the MD nucleus and pulvinar, in a study that found no significant effects by these measures in other thalamic nuclei (Kemether et al. 2003; Hazlett et al. 2004). The BG-recipient intralaminar thalamus expresses D2 dopamine receptors at particularly high density (Rieck et al. 2004), and these receptors are targeted by antipsychotic drugs, usually with ameliorative effect for positive symptoms (Nordström et al. 1993; Kay et al. 1987). There is evidence from experimental clinical practice that lesioning of the mediodorsal and rostral intralaminar nuclei can permanently eliminate delusions and somatosensory, auditory, and visual hallucinations associated with Sz, while rhythmic (20 and 50 Hz) electrical stimulation of these areas can abolish symptoms promptly (Hassler 1982).

That some hallucinations and visuospatial deficits in Sz may involve BG interaction with the intralaminar nuclei is further suggested by the common occurrence in PD of visual hallucinations (Barnes and David 2001) and impaired shifting and maintenance of visual attention (Wright et al. 1990). PD is marked by abnormally strong coupling within BG loops (Hammond et al. 2007) and extensive cell loss in the thalamus specific to the caudal intralaminar nuclei (Henderson et al. 2000). PD and Huntington's disease are both associated with voluntary saccade deficiencies, including abnormal distractibility in Huntington's (Bronstein and Kennard 1985; Lasker et al. 1987, 1988), resembling some of the oculomotor abnormalities associated with Sz.

Auditory hallucinations are commonly associated with Sz (de Leede-Smith and Barkus 2013; McCarthy-Jones et al. 2014), and many of the brain areas implicated in these hallucinations are within or intimate with the BG (Shergill et al. 2000). In cat, connections of the parafascicular nucleus with secondary auditory cortex and the anterior auditory field have been demonstrated (Scannell 1999), but as noted above, no direct connections have been found between the intralaminar nuclei and the primary and several adjoining auditory fields (Scannell 1999). This lacuna is intriguing, in that it suggests that intralaminar input may be detrimental to signal integrity there, outweighing the benefits that evolutionarily stabilize intralaminar innervation elsewhere. This indirectly provides further evidence that the relationship of the intralaminar nuclei to cortex is delicately balanced.

5.11. Disruption in schizophrenia of sleep spindling and prefrontal FSI activity likely grossly disrupt BGMS.

As noted above, sleep spindling, generating broadly synchronized responses in cortex, particularly implicates the BG-recipient intralaminar and association nuclei of the thalamus (Contreras et al. 1997). Spindling is thought to be crucial for consolidation during sleep of new associations (Tamminen et al. 2010; Genzel et al. 2014). Moreover, a direct association has been demonstrated between the prevalence of fast parietal spindles during stage 2 and slow wave sleep, and fluid intelligence (as distinguished from crystallized intelligence) (Fang et al. 2017).

A consistent pattern of deficient spindle activity in stage 2 sleep has been demonstrated in Sz, with severity of symptoms correlated to degree of deficiency (Ferrarelli et al. 2007, 2010a; Wamsley et al. 2012). Since synaptic homeostasis mechanisms largely operate at the level of individual microcircuits, neurons, and synapses (Turrigiano 2011), spindling deficits may cause progressive deterioration of the long range circuits that are the physiological basis of effective connectivity in wakefulness. Such deterioration is, in any case, characteristic of Sz (Lim et al. 1999; Mori et al. 2007; Collin et al. 2014; de Leeuw et al. 2015). As reviewed later, it is the hub areas of cortex that are most implicated in the circuit deterioration characteristic of Sz. These are the areas most clearly implicated in fluid intelligence, as explored later.

Sleep spindles have been found to preferentially recruit FSIs in PFC, more than pyramidal projection cells there (Peyrache et al. 2011). This is likely a consequence of feedforward inhibition in response to the lengthy ultra-high frequency bursts associated with spindling, importantly demonstrating that thalamocortical projections oppose both FSIs and pyramidal cells in cortex.
Impairment of GABA synthesis in intrinsic FSIs of DLPFC, and consequent deficiencies in cortical projection neuron synchronization and loosening of spike coincidence criteria, have been implicated in Sz (Lewis et al. 2005; Gonzalez-Burgos et al. 2015). PFC FSI response patterns are also modified by dopamine inputs (Tierney et al. 2008), which are abnormal in Sz (Grace 2016). The consequences of severe deficiencies in sleep spindling, simultaneous with disruption of feedforward inhibition by cortical FSIs, may disrupt BGMS with particular potency. Whether spindle and PFC FSI deficiencies are part of the etiology of Sz, or are sequelae, remains to be determined and may vary. It is probably significant that both can result directly from GABA dysfunction.

5.12. Reports on the functional correlations of the intralaminar nuclei, and their physiological relationships with the basal ganglia and cortex, likely supply some of the best available evidence supporting the BGMS model.

Evidence that the intralaminar nuclei are profusely innervated by the BG and integral to BG circuitry, that they are innervated by and proximally appose L5 pyramidal neurons, that these appositions are subject to stringent (<4 ms) coincidence requirements, and that spike bursts from highly energetic intralaminar neurons in a state of wakefulness last only 4-5 ms and recur at a rate of 20-40 Hz, suggest that BG output associated with well-practiced behavior and cognition is precisely aligned on this timescale. While the timing of spikes in projections to superficial cortex is surely significant, it is in the projections to somatic layers that timing appears most critical, and that the potential for timing-based selectivity is most apparent.

6. Delay Mechanisms in Basal Ganglia-Thalamocortical Circuits

In this section:

6.1. Oscillatory structure and frequencies in mammals are highly conserved, while fiber conduction velocities vary widely within and between species.

6.2. The basal ganglia must accommodate widely varying long range timing requirements.

6.3. Corticostriatal and striatopallidal delays are long and diverse, so that particular patterns of cortical activation can be focused on particular striatal, pallidal, nigral, thalamic, and cortical targets.

6.4. Pallidothalamic and thalamocortical delays are short and uniform.

6.5. Total delay from a corticostriatal neuron, through the basal ganglia direct path to thalamus, back to cortex, is roughly one gamma cycle through GPi, and one beta cycle through SNr.

6.6. Multiple mechanisms might underlie delay plasticity in paths from cortex to thalamus via the basal ganglia.

6.7. Learning and extinction establish and dissolve context-specific synchronous spike responses in the striatum.

6.8. Intralaminar thalamus and cholinergic striatal interneurons may be key components of the mechanism whereby the BG learn to generate context-appropriate synchronous output.

6.1. Oscillatory structure and frequencies in mammals are highly conserved, while fiber conduction velocities vary widely within and between species.

Among mammalian species, conduction velocities (CVs) for a given homologous projection vary widely, while alpha, beta, and gamma oscillatory frequencies are roughly constant, despite a 17,000-fold variability in brain volume (Buzsáki et al. 2013). Geometrically proportional scale-up of axonal propagation velocities appears to arrange for similar long range delays regardless of size, maintaining the compatibility of circuit synchrony mechanisms with the conserved and intrinsic dynamics of neurons and their microcircuits, with few exceptions (Buzsáki et al. 2013; but see Caminiti et al. 2009).

6.2. The basal ganglia must accommodate widely varying long range timing requirements.

The BG are as beholden to these stable neuronal dynamics as is the rest of the brain, but according to the BGMS model, they must additionally align their responses to meet the timing requirements in each learned combination of scenario, efferent area, and recipient area, necessitating enormous temporal flexibility and precision. The optimal delay for a particular circuit from cortex, through subcortical structures, to another area of cortex, varies significantly, reflecting both the dominant oscillatory
frequency of the cortical activity, and the non-zero delay of the implicated corticocortical projections (Gregoriou et al. 2009; Nowak and Bullier 1997). The mechanisms whereby the BG accommodate these diverse timing requirements likely endow them with particularly rich representational power: When similar arrangements in cortex were simulated, an unanticipated result was that the number of distinct ephemeral neuronal assemblies greatly exceeded the number of neurons, and might even exceed the total number of synapses in the network (Izhikevich 2006).

Importantly, neuromodulatory projections from the midbrain and basal forebrain project not only to cortex and thalamus, but extensively to the BG. Thus oscillatory acceleration in cortex and thalamus is likely accompanied by acceleration in the BG. This might arrange to preserve the applicability of timing relationships learned by the BG at widely varying levels of arousal.

Plasticity mechanisms in the central nervous system are exquisitely sensitive to timing relationships, at time scales of several or even fractional milliseconds within a ±20 ms window, so that in many neurons, faster paths of communication are consolidated, and slower paths are culled (Markram et al. 1997; Bi and Poo 1998, 2001; Song et al. 2000). Spike-timing-dependent plasticity (STDP) in conjunction with coherent oscillatory activity may build temporally coherent circuits by grouping axons with precisely matching delays (Gerstner et al. 1996). However, the relationship of these mechanisms to the delay of polysynaptic BG paths is unclear, and surely complicated, particularly given evidence that STDP in striatal SPNs is reversed (Fino et al. 2005).

In the BG, a more obvious substrate for meeting time alignment requirements is the enormous variety of paths, delays, and time constants among corticostriatal and striatofugal neurons and fibers. A multiplicity of paths, exhibiting a multiplicity of delays, may assure that for any two cortical loci, there exist polysynaptic paths to the implicated thalamocortical neurons, exhibiting nearly optimal delays, that need only be strengthened to effect learning of appropriately selective, timed, and directed responses.

6.3. Corticostriatal and striatopallidal delays are long and diverse, so that particular patterns of cortical activation can be focused on particular striatal, pallidal, nigral, thalamic, and cortical targets.

Corticostriatal fibers exhibit fairly slow average CV, measured to be about 3 m/s in macaque (delay range 2.6 - 14.4 ms), in marked contrast to corticopeduncular fibers, measured to average greater than 20 m/s (delay range 0.75 - 3.6 ms) (Turner and DeLong 2000). Striatopallidal fibers are markedly slower still, measuring under 1 m/s in macaque (Tremblay and Filion 1989). The typical striatopallidal CV is so low that at peak spike rate (~80 Hz (Kimura et al. 1990)), apparently more than one action potential can be propagating simultaneously on the same axon. Not only are corticostriatal and striatopallidal/striatonigral CVs notably slow, the implicated delays are also highly varied. In a study of macaques investigating paths through the Gpi (Yoshida et al. 1993), delays from the caudate and putamen portions of the striatum to Gpi averaged 16.5 ± 7.9 ms and 10.4 ± 7.4 ms respectively, and overall delays of the corticostriatopallidal path from motor cortex to Gpi (identified as the studied cortical area with shortest delay) averaged 15.5 ± 4.2 ms. A subsequent companion study investigating the paths through the SNr (Kitano et al. 1998) found even greater delays and variance; delays from the caudate and putamen to SNr averaged 22.8 ± 16.2 ms and 17.9 ± 7.7 ms respectively, and delays from frontal cortex to caudate nucleus averaged 18.8 ± 5.7 ms, ranging from 7-31 ms. Combined delay of the corticostriatonigral path was 39.8 ± 14.8 ms, ranging from 12-90 ms, spanning nearly a full order of magnitude. These figures likely do not reflect additional delays associated with the interposition of striatal FSIs. As reviewed later, FSIs likely determine the precise timing of SPN spikes. Thus, this additional delay is meaningful in the BGMS model.

It is significant that CVs are slow and diverse in both the corticostriatal and striatopallidal/striatonigral projections. Locus-specific phase disparities, associated with converging corticostriatal inputs from widely separated but functionally connected loci, can be compensated by distinct conduction delays in their respective corticostriatal projections. Activation of a multi-areal cortical ensemble can then produce spatiotemporally coincident spiking in FSIs and SPNs, despite phase skews in the ensemble at the cortical level. In essence, the spatiotemporal pattern of activation in cortex is convolved with the function embodied by the corticostriatal projection, so that particular cortical activation patterns are focused on particular cells in the striatum, which can learn to respond to them. Separately and subsequently, the output from SPNs is subjected to slow and diverse CVs in the striatopallidal projection, by which substantial and variable delays can be applied to BG input to the thalamus. By these delays, according to the BGMS model, BG output spikes are temporally aligned to promote thalamocortical activity associated with selected connections, and inhibit competing activity. Diverse striatopallidal delays also allow for coactivated SPNs to align their inputs to jointly targeted pallidal and thalamic cells.

As mentioned above, the STDP of SPNs is apparently reversed: synapses are strengthened that activate in the ~20 ms after activity in other synapses has induced postsynaptic discharge, and synapses are weakened that bear activity in a similar time window preceding discharge (Fino et al. 2005). This arrangement seems to systematically maximize the delay of paths through
striatum, though its true function may be to maximize the variety, and the consequent breath of associativity, of SPN afferents. Striatal FSIs show normal STDP relations, tending to minimize delays by strengthening the synapses that bear the earliest activity correlated with discharge (Fino et al. 2008). Striatal physiology thus appears to promote dispersion, while minimizing the delay of FSIs, which—as reviewed later—consistently activate before SPNs in their vicinity, and precisely control the timing of SPN discharge through powerful appositions.

6.4. Pallidothalamic and thalamocortical delays are short and uniform.

Consistent with the proposition that pallidothalamic and nigrothalamic axons collateralize to orchestrate long range synchronies via the thalamus, the delay of these segments is comparatively short and uniform: in macaques, antidromic response from thalamus to SNr was found to average 1.56 ± 0.44 ms (Kitano et al. 1998), and an earlier study (Harnois and Filion 1982), on squirrel monkeys, found similar antidromic delays from thalamus to GPI, tightly clustered about an average of 1.3 ms from VA-VL sites, and 1.6 ms from CM sites, arising from a CV of 6 m/s. Similarly, as noted earlier, the thalamocortical projection appears to be tuned for rapidity and exquisitely precise (sub-millisecond) alignment of the projection to any given area of cortex; selective myelination of the portion of thalamocortical axons within cerebral white matter, the length of which varies two-fold within a target area, appears to account for this (Salami et al. 2003). In cats, the delays for antidromic stimulation of thalamocortical projections from VA-VL and VM thalamic nuclei to Brodmann areas 4, 6, 8, and 5 were found to average from 2.3 ms (VA/VL to area 4, primary motor) to 4.2 ms (VM to area 8, motor association cortex), with almost all measured delays falling below 6 ms, and significant and systematic, but small, shifts in delay as a function of thalamic nuclear origin (Steriade 1995).

6.5. Total delay from a corticostriatal neuron, through the basal ganglia direct path to thalamus, back to cortex, is roughly one gamma cycle through GPI, and one beta cycle through SNr.

The total average conduction delay from cortex, through the BG direct path (neglecting striatal FSI interposition), to thalamus, and back to cortex, is about 20 ms for a typical path through GPi and VA/VL interposition, and about 45 ms for a typical path through SNr to a frontal eye field in area 8, and the range of possible delays is enormous, roughly 15-25 ms and 30-60 ms respectively for average ± one standard deviation. Put differently, for that statistical interval, the cumulative conduction delay for a round trip from cortex through the BG via the GPi corresponds to one full cycle of gamma oscillation at 40-

67 Hz, and the delay of that round trip via the SNr corresponds to one full cycle of beta at 17-33 Hz. These relationships suggest that cortical activity routed through the BG and thalamus is typically delayed by a single cycle upon its return to cortex, but perhaps in some scenarios higher frequency oscillation is delayed by two or more cycles. This might be viewed as a kind of cross-frequency coupling, and might involve cross-frequency interactions in the SNr.

6.6. Multiple mechanisms might underlie delay plasticity in paths from cortex to thalamus via the basal ganglia.

Fine tuning of BG path delays may be possible within the spatially extensive terminal and dendritic processes of corticostratial (Mailly et al. 2013) and striatopallidal (Levesque and Parent 2005) neurons. In particular, striatopallidal axons penetrate perpendicular to the dendritic disks of pallidal output neurons, emitting thin unmyelinated (hence particularly low CV) collaterals parallel to the disks, repeatedly synapsing with the same target neuron (Goldberg and Bergman 2011). Localized, selective strengthening of these appositions might adjust the path delay in natural response to reinforcement.

Axonal CV plasticity, which has only recently been appreciated (Fields 2015), is largely unknown in its mechanistic particulars, but might also operate in the BG.

Whether optimization of conduction delays is by competition between distinct fiber paths, or between distinct synapses along the same fiber path, reinforcement-driven persistent modulation of synaptic efficacy could optimize not only the output rates (the efficacy with which a particular input evokes an output), but the fine time structure of the outputs, to the degree that reinforcement is a function of fine time structure. Axonal CV plasticity might operate in conjunction with these mechanisms, responding to the same reinforcement signals. Moreover, the traversed neurons themselves may exhibit a diversity of intrinsic time constants, similar to an arrangement that has been described in PFC (Bernacchia et al. 2011). Indeed, the activation of both PFC and striatal neurons shows a finely graded diversity of delays, though path variety may be the underlying mechanism (Jin et al. 2009).

6.7. Learning and extinction establish and dissolve context-specific synchronous spike responses in the striatum.

In rats trained on a maze task until habit formation, then given extinction training, and finally retrained on the original task, ensembles of SPNs in the dorsal striatum formed, narrowed, and changed their responses to fire synchronously at the beginning and end of the task, then reverted, and finally reestablished their synchronous responses, respectively, with a high correlation of response synchrony to behavioral performance (Barnes et al. 2005).
Similarly in monkeys, over the course of self-initiated, reward-motivated learning, large numbers of neurons in the dorsal striatum developed phasic responses aligned with the beginning and end of saccade sequences (Desrochers et al. 2015). In rat ventral striatum, a shift in the patterns of phasic activity from local islands of high gamma synchrony, to beta synchrony spanning wide areas and both SPNs and FSIs, accompanies skill acquisition and habit formation (Howe et al. 2011). These studies provide strong evidence that striatal plasticity entails the formation of widely distributed constellations of FSI-SPN assemblies that learn to discharge in synchrony as a function of context.

### 6.8. Intralaminar thalamus and cholinergic striatal interneurons may be key components of the mechanism whereby the BG learn to generate context-appropriate synchronous output.

Presumed cholinergic interneurons in the striatum, recognized electrophysiologically by their tonic firing patterns, may be key components of a time alignment learning mechanism in the BG. Over the course of skill acquisition, progressively larger proportions of these sparsely distributed interneurons, over very wide areas of striatum, have been seen to pause in brief, precise synchrony in response to salient sensory stimuli, with this response dependent on dopamine supply (Graybiel et al. 1994). These interneurons have been implicated in the learning of changes in instrumental contingencies, with learning dependent on activity in thalamostriatal projections originating in the intralaminar nuclei (Bradfield et al. 2013). Moreover, precisely synchronized stimulation of these interneurons directly induces dopamine release through cholinergic receptors on dopaminergic axons, independent of somatic activation of midbrain DA neurons (Threlfell et al. 2012), suggesting that synchrony per se, as measured by activity in intralaminar afferents, is intrinsically reinforced in the striatum.

As noted earlier, striatal matrix is extensively and preferentially targeted by inputs from intralaminar thalamus, apposing both SPNs and FSIs. Thus, mechanisms of striatal plasticity are positioned to monitor and respond to the synchronies that the BG generate in thalamus, and so presumptively in cortex. Dopamine-dependent and dopamine-inducing activity in striatal cholinergic interneurons, innervated by these thalamostriatal projections, might act to strengthen striatal synapses that contribute to the production of synchronous thalamocortical activity associated with reward. Related mechanisms may similarly drive plasticity in other BG structures targeted by the intralaminar nuclei, notably the GP and STN (Sadikot et al. 1992a).

### 7. The Basal Ganglia as a Flexible Oscillation Distribution Network

**In this section:**

7.1. BGMS entails the coherent transmission of cortical spike volleys through the basal ganglia.

7.2. Activity in a single corticostratal neuron can influence activity in large expanses of cortex in a single loop through the basal ganglia.

7.3. Afferents from interconnected cortical areas converge in the striatum.

7.4. Convergence in the striatum of afferents from interconnected cortical areas intrinsically arranges to distribute oscillatory reference signals through open loops back to cortex.

7.5. Striatal FSIs are tightly coupled to projection neurons in cortex and striatum, and FSI activity is idiosyncratic and independent.

7.6. Striatal FSIs regulate the spike timing of SPN activity, with profound and apparently causal impact on behavior.

7.7. Striatal FSI physiology facilitates high fidelity relay.

7.8. The projection from cortex to striatal spiny projection neurons is massively convergent, and SPNs fire only when their inputs are substantial and synchronous, reflecting robustly synchronized cortical activity.

7.9. Striatal projection neuron activation during resting wakefulness is sparse.

7.10. SPNs exhibit no frequency preference, but the fine timing of an SPN's activity can be determined by that of a narrow and dynamic subset of its excitatory afferents.

7.11. SPNs are almost entirely independent of each other.

7.12. The striatopallidal projection is massively convergent.

7.13. Striatal input to BG output neurons controls their timing, and coherency in afferent activity to BG output neurons may be crucial to their effective activation.

7.14. Direct path output neurons are tonically and phasically independent in the normal brain.

7.15. The pallidothalamic projection is powerful, and its constituent axons are especially divergent.

7.16. The BG-recipient thalamic projection to cerebral cortex is massively divergent.
7.1. BGMS entails the coherent transmission of cortical spike volleys through the basal ganglia.

BGMS crucially entails the coherent transmission of corticostriatal spike volleys, through BG and thalamic relays, back to cortex, with routing and delays providing for spatiotemporal coincidence with corticocortical spike volleys associated with the selected effective connections. Above is a discussion of the various mechanisms that might underlie these temporal alignments. Below, I discuss the myriad patterns of convergence and divergence in the BG that underlie the capacity of the BG to distribute spike volleys coherently, widely, flexibly, and specifically.

7.2. Activity in a single corticostriatal neuron can influence activity in large expanses of cortex in a single loop through the basal ganglia.

Divergence in the paths from corticostriatal neurons through striatal fast spiking interneurons and spiny projection neurons, pallidal and nigral projection neurons, and thalamocortical neurons projecting to superficial cortex, suggest geometric expansion of activity from a single cortical column to a scope encompassing large areas of cortex. Well over $10^5$ cortical neurons might be influenced by the output of a single striatally projecting neuron in cortex. The axonal processes of each corticostriatal neuron distribute sparsely through large regions of striatum, spanning on average 4%, and up to 14%, of total volume, forming on average ~800 synaptic boutons, likely apposing nearly as many distinct striatal neurons (Zheng and Wilson 2002). While more than 90% of striatal neurons are spiny projection neurons, 3-5% are fast spiking interneurons (Koós and Tepper 1999). If corticostriatal neurons innervate SPNs and FSIs with similar preference, this suggests that each innervates on average ~24 FSIs (though there are indications of specialization in corticostriatal targeting of FSIs (Ramanathan et al. 2002)). Each FSI projects to ~300 SPNs (Koós and Tepper 1999), each SPN projects to ~100 pallidal neurons (Yelnik et al. 1996; Goldberg and Bergman 2011), each pallidal neuron projects to ~250 thalamic neurons (Parent et al. 2001), and each thalamic neuron projects to more than 100 cortical neurons (Parent and Parent 2005) (likely far more (Rubio-Garrido et al. 2009)). With a cortical neuron population in lower primates of approximately $10^9$ (Herculano-Houzel et al. 2007; Azevedo et al. 2009), these divergence ratios suggest that a single corticostriatally projecting neuron can influence all of the cortical neurons within the relevant bounds of segregation. This influence is further fortified by intrinsic mechanisms in superficial cortical layers, described earlier, that horizontally spread oscillations.

7.3. Afferents from interconnected cortical areas converge in the striatum.

As emphasized earlier, interconnected cortical regions systematically converge and interdigitate, even while the projection of each cortical region diverges in a spotty, widely distributed pattern (Van Hoesen et al. 1981; Selemon and Goldman-Rakic 1985; Parthasarathy et al. 1992; Flaherty and Graybiel 1994; Hintiryan et al. 2016). Direct path SPNs are preferentially innervated by neurons in cortex that are reciprocally interconnected over long ranges at the single unit level (Lei et al. 2004; Morishima and Kawaguchi 2006). Convergence of densely interconnected cortical areas to single FSIs is common; a study in rats found that nearly half of FSIs innervated by primary somatosensory or primary motor cortex receive projections from both (Ramanathan et al. 2002). Moreover, FSIs show a significant preference for direct path SPNs, with functional connectivity demonstrated for roughly half of identified direct path FSI-SPN pairs, but roughly a third of indirect path pairs (Gittis et al. 2010).

7.4. Convergence in the striatum of afferents from interconnected cortical areas intrinsically arranges to distribute oscillatory reference signals through open loops back to cortex.

As reviewed earlier, synchronization of activity in two areas signifies that those areas are functionally connected, and asynchrony or antisynchrony signifies functional disconnection. This prompts the expectation that functionally connected areas projecting convergently to an FSI robustly entrain that FSI, which imparts their shared cortical rhythm to the SPNs it innervates. By this mechanism, effective connections might act through the BG to directly excite further connections, or to inhibit connections, as envisioned by von der Malsburg (1999). On the other hand, when the afferents to an FSI are active but unsynchronized, the FSI is likely arrhythmicly activated, imparting an incoherent inhibitory spike pattern to those SPNs, thereby preventing rhythmic discharge. Indeed, as noted earlier, individual cortical cells subject to conflicting synchronies are themselves likely to exhibit arrhythmic spiking patterns (Gómez-Laberge et al. 2016). Antisynchronized afferent activity might have similar results, activating the FSI at twice the fundamental frequency, likely imparting a spike pattern to the SPNs that is particularly efficient at inhibiting discharge. In a third mode of operation, afferents to the FSI from one area bear strong oscillatory activity, while other afferents bear significantly weaker activity that may or may not be rhythmic. In this case, the FSI might impart the strong oscillatory activity to the SPNs, while the weak afferent activity has relatively little effect on FSI spiking, so that
strong localized cortical oscillation is selected for effective connection to other areas.

7.5. Striatal FSIs are tightly coupled to projection neurons in cortex and striatum, and FSI activity is idiosyncratic and independent.

The physiology of striatal FSIs in normal behaving animals, and their relationships with cortical and striatal projection neurons, are complex, specialized, and nuanced (Berke 2011). The temporal structure of FSI spiking closely conforms to that of afferent activity, aligning precisely with the trough of extracellular afferent LFP, regardless of band (Sharott et al. 2009, 2012). The phasic activation of each FSI is strongly but idiosyncratically related to ongoing behavior, and in particular, is independent of activity in other FSIs (Berke 2008). Nearly half of corticostriatal synaptic inputs to FSIs are robust, apposing somata or proximal dendrites (Lapper et al. 1992), and corticostriatal axons commonly form several synaptic boutons targeting a single FSI, indicating selective innervation and stronger coupling (Ramanathan et al. 2002). Consistent with the observed idiosyncrasy and independence of FSI responses to cortical activity, synaptic inputs to FSI somata are few, and FSI dendrites are almost entirely devoid of spines (Kita et al. 1990)

7.6. Striatal FSIs regulate the spike timing of SPN activity, with profound and apparently causal impact on behavior.

FSI projections to SPNs are robust (Koós and Tepper 1999), but FSI activation has been found to modulate SPN activity, rather than simply inhibiting or releasing it (Gage et al. 2010). In behaving rats, FSIs and nearby SPNs are simultaneously active in various stages of task learning and performance, at precisely opposite phases, at both beta and gamma frequencies (Howe et al. 2011). Simulation of normal in vivo conditions in the striatum shows formation of small assemblies of synchronized SPNs, with FSI activation increasing the firing rates of connected SPNs (Humphries et al. 2009). Pharmacological blockade of FSIs in sensorimotor striatum does not substantially change the average firing rates of nearby SPNs, but induces severe dystonia (Gittis et al. 2011), demonstrating that FSI regulation of the temporal structure of SPN activity is crucial to normal behavior.

FSIs exhibit significantly lower firing thresholds than do SPNs relative to the intensity of cortical activity; consequently, activation of SPNs is preceded by, and spatially embedded within, an encompassing area of activated FSIs governing their output (Parthasarathy and Graybiel 1997). In a study inducing focused, synchronized activity in primary motor cortex, nearly all (88%) of the FSIs in the center of the zone of striatal activation were activated, and nearly as many (78%) of the FSIs in a penumbra were activated; FSIs showed a robust and disproportionate response, comprising 22% of the responding striatal neuron population, while representing <5% of striatal neurons (Berretta et al. 1997).

It has been shown in awake behaving rats that the activity of FSIs in the sensorimotor striatum rises shortly before, and peaks during, initiation of behavior reflecting a decision, and that FSI activity precedes that of coactivating neurons in primary motor cortex (Gage et al. 2010). Further underscoring the prominence of FSIs in regulating behavior, Tourette syndrome is associated with abnormally low density of presumed FSIs in the striatum (Kalanithi et al. 2005). Indeed, the cancellation of inapt behaviors has been associated with GABAergic feedback projections from the GPe that selectively target FSIs (Mallet et al. 2016; Deffains et al. 2016). In the normal brain each SPN is apposed by several FSIs (Koós and Tepper 1999); pathological sparseness in FSI afferents to an SPN might result in entrainment of that SPN to cortical activity that would normally be inhibited by another FSI. The resulting spurious SPN discharges, phase-locked to localized cortical activity, then might induce spurious connections in cortex, manifesting as tics and other compulsions.

FSIs are electrically woven together into a loose, sparse continuum by gap junctions (Kita et al. 1990; Koós and Tepper 1999), that in simulation modestly encourage synchronization of neighboring FSIs, while modestly damping their activity unless afferent activity is well-synchronized (Hjorth et al. 2009). This further suggests an arrangement in which FSIs operate as a matrix, comprehensively regulating the temporal structure of SPN spike activity, with particular sensitivity to synchrony in the corticostriatal projection. Each SPN receives inputs from several (estimated 4-27) FSIs (Koós and Tepper 1999), suggesting that FSI recruitment in a striatal neighborhood reliably imparts strong modulatory input to all of the SPNs in that neighborhood.

While there is some evidence that FSI prevalence in the striatal population follows a gradient, with highest concentration in the dorsal and lateral striatum and lowest in the medial and ventral striatum (Kita et al. 1990; Bennett and Bolam 1994; Berke et al. 2004), more recent evidence demonstrates FSI effects and connectivity in VS similar to those in dorsal striatum (Taverna et al. 2007; Howe et al. 2011), and the appearance of a striatal FSI density gradient may be an artifact of spatially correlated cytological heterogeneity in the FSI population (Tepper et al. 2008).

7.7. Striatal FSI physiology facilitates high fidelity relay.

Striatal FSIs contain parvalbumin, can sustain firing rates of 200 Hz with little or no adaptation, have narrow action potentials (less than 500 µs), do not feed back to the inputs of other FSIs, and do not receive inputs from SPNs (Koós
and Tepper 1999; Mallet et al. 2005; Taverna et al. 2007). SPNs and FSIs produce similar inhibitory post-synaptic currents (Koós et al. 2004), but FSI inputs to SPNs are directed to somata and proximal dendrites, where they can exert a more decisive and precise effect on the target, whereas corticostriatal inputs to SPNs, and SPN inputs to other SPNs, are directed to distal dendrites (Bennett and Bolam 1994). SPNs may exhibit a low pass characteristic (Stern et al. 1997), so that even while the SPNs are highly sensitive to synchrony in their excitatory afferents (discussed below), the fine timing of the spikes they produce could be determined almost entirely by the FSIs. The influence of FSIs on the SPNs they target entails not only retardation of SPN phase, but phase advancement, through a rebound effect that reduces the firing threshold of the targeted SPN; the effect is most pronounced 50-60 ms after the FSI spike; SPN depolarization is advanced by ~4 ms when FSI spikes reach the SPN 30-70 ms before excitatory afferent spiking reaches the SPN (Bracci and Panzeri 2005).

7.8. The projection from cortex to striatal spiny projection neurons is massively convergent, and SPNs fire only when their inputs are substantial and synchronous, reflecting robustly synchronized cortical activity.

Convergence is anatomically inescapable in paths through cortex, striatum, and pallidum. There are roughly ten times as many pyramidal cells in cortex projecting to the striatum, as there are medium spiny projection neurons, with each SPN afferented by roughly 10,000 distinct cortical neurons (Kincaid et al. 1998; Zheng and Wilson 2002). The enormous convergence to single SPNs, and their high firing threshold, arrange so that SPNs fire only when their afferent activity is substantial, synchronous, and distributed broadly across dendrites (Zheng and Wilson 2002). As noted earlier, the sensitivity of the striatum to synchrony in its inputs is particularly consequential if striatal output induces synchronies (as in the BGMS model), because the striatum is then positioned to iteratively process information encoded as patterns of synchrony.

Though relatively sparse, corticostriatal projections from GABAergic interneurons to SPNs (Melzer et al. 2017), particularly from cortical FSIs, are an additional mechanism that may regulate SPN sensitivity to synchrony. As noted earlier, cortical FSIs have been shown to be part of a coincidence detection mechanism with a very narrow window (Pouille and Scanziani 2001). Depending on the pattern of apposition of these cortical FSIs, they might also function like striatal FSIs, precisely controlling the timing of SPN output, as described above.

7.9. Striatal projection neuron activation during resting wakefulness is sparse.

Corticostriatal neurons seldom fire periodically, but rather, their activity is aperiodic but phase-locked to oscillation in their cell membranes (Stern et al. 1997); thus their converged input to SPNs can exhibit substantial periodicity, but only when cortical activity is robust and synchronized. The aperiodicity, low spontaneous rates, and narrowly discriminative activity of individual corticostriatal neurons, suggest that few SPNs will be active at a given moment, and many will be silent (Turner and DeLong 2000). In the awake, resting animal, a large majority of SPNs are silent (Sandstrom and Rebec 2003), and some SPNs remain silent even in the awake, behaving animal, with no apparent physiological distinctions to explain the silence (Mahon et al. 2006).

7.10. SPNs exhibit no frequency preference, but the fine timing of an SPN’s activity can be determined by that of a narrow and dynamic subset of its excitatory afferents.

SPNs exhibit no persistent or membrane-intrinsic frequency preference; rather, the aggregate intensity of afferent activity (simulated in vitro by injection of constant current) establishes a firing rate, and the phase of that firing preferentially follows that of afferent components at frequencies near the established rate, with particularly sharp frequency selectivity at beta frequencies (Beatty et al. 2015). This signifies that, as the aggregate afferent activity to an SPN increases to and beyond the firing threshold, the phase of that firing will be preferentially determined by progressively higher-frequency synchronized components of that afferent activity. The functional significance of this arrangement is unknown, but might be relevant to scenarios in which an SPN is not subject to regulation by FSIs (if such scenarios occur at all in the normal striatum, which seems doubtful), and in any case seems to be a virtually inevitable biophysical dynamic.

7.11. SPNs are almost entirely independent of each other.

SPNs exhibit uncorrelated activity even when they are immediate neighbors, suggested to be due to an arrangement in which each SPN receives axons from a unique, sparse subset of corticostriatal neurons (Kincaid et al. 1998; Zheng and Wilson 2002; Wilson 2013). This also follows from the firing patterns of direct path corticostriatal neurons, which are highly idiosyncratic (Turner and DeLong 2000). SPN axon collaterals synapse upon the distal dendrites of other SPNs, with each SPN inhibited by up to 500 other SPNs, but these inputs are sparse, weak, unreciprocated, and asynchronous, and do
not induce correlated activity among neighborhoods of interconnected SPNs (Tepper et al. 2008; Wilson 2013). Instead, their location suggests they interact with excitatory afferents, enhancing the combinatorial power of the corticostratial and thalamostriatal projection systems.

7.12. The striatopallidal projection is massively convergent.

Convergence in the projections from striatum to the pallidal segments and SNr is inevitable given the further reduction in volume and cell count. In human, volume ratios from the striatum are 12:1 to the GPe, 21:1 to the GPi, 24:1 to the SNr, and 6:1 from the striatum to GPe, GPi, and SNr combined (Yelnik 2002), with cell count ratio estimates of 97:1, 400:1, and 210:1, respectively, for a combined ratio of 57:1 overall, and 138:1 in the direct path (Kreczmannski et al. 2007; Hardman et al. 2002). In rats, the volume ratios are 7:1, 112:1, and 19:1, for GPe, GPi (EP), and SNr, respectively, for a combined ratio of 5:1, and the cell count ratio estimates are 61:1, 880:1, and 106:1, respectively, for a combined ratio of 37:1 (Oorschot 1996).

Each pallidal projection neuron forms a large 1.5 mm² dendritic disk perpendicular to incident striatopallidal axons, innervated by 3,000-10,000 SPNs (Yelnik et al. 1984; Goldberg and Bergman 2011). The dendritic processes of projection neurons in the SNr have variable forms, with an extent similar to that of pallidal dendrites, resulting in similar convergent innervation by SPNs (François et al. 1987). These arrangements imply a notional convergence ratio from corticostratial neurons, to SPNs, to pallidial projection neurons, as high as 10⁸. There is only slight convergence in the pallidothalamic projection, but extensive convergence in the thalamocortical projection (Rubio-Garrido et al. 2009) suggests a notional convergence ratio substantially greater than 10⁹ for the full loop back to cortex.

The striatopallidal projection, like the corticostratial projection, also entails divergence. Each SPN axon forms 200-300 synapses, sparsely distributed through a large volume of pallidum, with 1-10 synapses formed with a given pallidum dendrite (Yelnik et al. 1996; Goldberg and Bergman 2011), implying that an SPN projects to 20-300 pallidal neurons. Moreover, with a tracer injection in the striatum encompassing a small cell population, a hundredfold increase is seen in the volume of pallidum labeled by the tracer, while larger injections increase the density, but not the volume, of the labeled area (Yelnik et al. 1996), confirming an arrangement of simultaneous, extensive divergence and convergence like that of the corticostratial projection.

Experiments in primates show that the projection from striatum to the GPi entails reconvergence, such that divergence in the projection from a cortical locus to multiple loci in the striatum is followed by convergence from those striatal loci to a single pallidal locus (Flaherty and Graybiel 1994). Graybiel (1998) suggested that the striatum thus acts as a dynamically configurable hidden layer. The BGMS model further proposes that this arrangement subserves selection and activation of effective connections in cortex. The path from a cortical locus, by diverging to many distinct FSI neighborhoods, then reconverging to a single pallidal locus, can be subjected to any of a variety of spike timings, representing a variety of candidate effective connections, while suppressing action through that pallidal locus when multiple SPNs impart conflicting activity upon it, as suggested above.

7.13. Striatal input to BG output neurons controls their timing, and coherency inafferent activity to BG output neurons may be crucial to their effective activation.

Experiments in vitro demonstrate that striatal afferents to GP can control the timing and precision of firing by the targeted cells, and that these cells can follow striatal oscillatory inputs up to the gamma range (Rav-Acha et al. 2005; Stanford 2002).

The relationship of FSIs to SPNs may help elucidate the role proposed for the BG in competitive selection (Redgrave et al. 1999). An output neuron in GPi or SNr bombarded by mutually incoherent SPNs would be incapable of imparting a coherent temporal pattern to its thalamic targets. If coherency in this path is crucial, as suggested by the BGMS model, then only those GPi/SNr neurons with predominantly coherent activity in their afferents can participate in activation of a motor or cognitive connection, while activation of clashing connections tends to be suppressed.

GPi activity increases when direct path SPNs are activated, and decreases when indirect path SPNs are activated, even while direct and indirect path activation are associated with widespread cortical activity increases and decreases, respectively (Lee et al. 2016). As repeatedly emphasized in this paper, this suggests that oscillatory modulation by spike-timing-dependent gain is among the core functions of the GABAergic output neurons of the BG direct path.

7.14. Direct path output neurons are tonically and phasically independent in the normal brain.

Spike timing within, and activation of, pallidal output neurons is almost completely independent (Nini et al. 1995; Nevet et al. 2007), so any coordination or synchronization must be sparsely distributed. Preliminary results noted earlier, from a study of functionally connected cortical, pallidal, and thalamic areas, demonstrates as much, with strong phasic correlation of LFPs but almost no correlation of individual neuron spiking with those LFPs (Schwab 2016, chapter 5). According to the BGMS model, broadly and densely
synchronized BG output would produce spurious and pathologically persistent effective connectivity in cortex, arresting task progress. As noted earlier, BG output neurons act intrinsically as independent oscillators; this arrangement breaks down in parkinsonism, in which task progress is retarded or arrested (Stanford 2002; Wilson 2013; Deister et al. 2013; Hammond et al. 2007; Nevet et al. 2007).

PD has been shown in magnetoencephalography studies to be associated with progressively greater functional connectivity in cortex, determined by measures of synchronization likelihood, both intra- and inter-areal, in both the alpha and, in moderate and advanced disease, the beta bands (Stoffers et al. 2008). It is also associated with disruption and progressive inefficiency of functional connectivity (Olde Dubbelink et al. 2014). Pathological synchrony in parkinsonism may be rooted in the striatum: in vitro experimentation with, and physiologically realistic simulation of, the dopamine-depleted striatum has demonstrated spontaneous pervasive formation of clusters of synchronized SPNs (Humphries et al. 2009).

### 7.15. The pallidothalamic projection is powerful, and its constituent axons are especially divergent.

The main BG output projections from GPi and SNr appose neurons in thalamus in giant inhibitory terminals, with multiple synapses, exerting powerful and precise inhibitory control of individually targeted cells, with GPi and SNr projections well-compartmented from each other (Bodor et al. 2008). Many of these projection neurons contain parvalbumin, with especially high density in the dorsal GP (Cote et al. 1991).

Pallidal axons branch extensively within thalamus, into 10-15 collaterals with highly confined terminal varicosities (Parent et al. 2000), so that each pallidal neuron projects to 200-300 neurons in thalamus; these are the most widely arborized neurons in the BG (Parent et al. 2001). The somata and primary dendrites of GPi- and SNr-recipient thalamocortical neurons outside the intralaminar nuclei are contacted almost exclusively by these afferents, with very dense terminal processes, suggesting that the GPi and SNr exercise predominant control over activity in these cells (Kultas-Ilinsky and Ilinsky 1990; Ilinsky et al. 1997). As discussed earlier, BG projections to the intralaminar thalamus do not follow this pattern, but instead predominantly appose small and medium dendrites (Sidibé et al. 2002).

In the pallidothalamic projection, a degree of convergence on single thalamocortical cells has been noted (Ilinsky et al. 1997). As suggested earlier, convergence of independently oscillating pallidal projection neurons produces aggregate input that bears the characteristics of Gaussian noise, so that pallidal output can reflect inputs to pallidum with high fidelity. This may be a crucial advantage that evolutionarily stabilizes this arrangement in mammals, which have a surficial cerebral cortex and closely aligned thalamocortical conduction delays (Salami et al. 2003; Steriade 1995), whereas in birds, there is no surficial cerebral cortex, and thalamic projection cells receive only a single calyceal BG input (Luo and Perkel 1999).

Given the high typical tonic discharge rate of pallidal and nigral neurons, thorough disinhibition or entrainment of targeted thalamocortical neurons requires coordination of multiple pallidal projection neurons. As with the convergence of several striatal FSIs on a single SPN, this suggests several activation scenarios. If all BG output neurons targeting a thalamocortical projection neuron are phasically silenced coincidentally, their common target might be activated synchronous with corticothalamic input. If instead those several inputs remain active, but are phasically synchronized, this would likely entrain their common target, even in the absence of corticothalamic input, and with great vigor in the presence of excitatory input exhibiting the favored frequency and phase. In a third scenario, some of the inputs are phasically silenced, coincident with others that are phasically synchronized, with the likely result that their common target is entrained by the active BG inputs. Until one of these coordinated arrangements is learned, modulation of one or several inhibitory afferents likely has lesser but significant postsynaptic effects, which might bootstrap learning in paths associated with the other afferents.

The dynamic in the intralaminar thalamus is somewhat different: because pallido- and nigrothalamic terminals there predominantly appose dendrites, their likely effect is to modulate receptivity to particular corticothalamic inputs with which they share a dendrite, so that only those inputs with the selected timing can affect the soma and, consequently, affect the somatically targeted L3 and L5 pyramidal neurons. As suggested earlier, this arrangement may maximize combinatorial power in the relationship of the BG to the intralaminar thalamus.

### 7.16. The BG-recipient thalamic projection to cerebral cortex is massively divergent.

The path from BG-recipient thalamus back to cortex exhibits striking divergence. As reviewed earlier, neurons of the rat VL, VA, and VM nuclei project profusely and with massive overlap to L1, with individual neurons collateralizing to widely separated areas (Rubio-Garrido et al. 2009; Kuramoto et al. 2009), and the intralaminar nuclei innervate nearly the entire cerebral cortex (Van der Werf et al. 2002; Scannell 1999). CM and PF axons that reach cortex arborize diffusely and widely, with a single axon from CM forming on average over 800 synaptic boutons in cortex, a count that may miss many poorly stained axonal processes in L1 (Parent and Parent 2005). Even considering the possibility of extensive multiple terminations on the same target neuron, which is relatively
unlikely in a diffuse projection, the number of cortical neurons innervated by a single BG-recipient thalamocortical neuron might be conservatively estimated at >100. As estimated above, the cumulative notional divergence ratio from a single corticostriatal neuron, through striatal FSIs, SPNs, pallidal projection neurons, and thalamocortical neurons, may exceed $10^9$.

8. The Direct, Indirect, and Striosomal Paths in the Regulation of Cortical Dynamics

In this section:

8.1. The regulation of cortical dynamics implicates all BG circuitry, and the striatum is the linchpin.
8.2. SPNs in the direct path are preferentially innervated by cortical neurons with reciprocal corticocortical connectivity.
8.3. BG output to thalamus arises from activity in relatively superficial cortical layers, and passes exclusively through striatal matrix, while striosomes receive input from relatively deeper layers, with areal distinctions.
8.4. Cholinergic, serotonergic, and dopaminergic localization to striatal matrix suggest specialization for dynamic, high fidelity processing of oscillatory signals.
8.5. A pattern of differential innervation in the direct path suggests specialization for integration and motivated action.
8.6. Cortical inputs to the direct path appear to be an exquisitely context sensitive sparse code, with relatively high divergence-convergence.
8.7. The direct and indirect paths, and striatal matrix and patch compartments, are neither crisply distinct nor mutually exclusive.

8.1. The regulation of cortical dynamics implicates all BG circuitry, and the striatum is the linchpin.

While BGMS as discussed in this paper most directly implicates the direct path, BG circuitry beyond the direct path is just as functionally crucial, and indeed is even more extensive and broadly connected than the direct path. The striatum is the common component in all these circuits. The striatum is a particularly complex brain organ, structured simultaneously along multiple schemes overlaid upon, and interacting with, each other in intricate patterns (Graybiel 1990; Kreitzer 2009; Tepper et al. 2010; Bolam et al. 2000). Its striosome-matrix dichotomy, and its direct-indirect dichotomy, both bear upon the present hypothesis.

8.2. SPNs in the direct path are preferentially innervated by cortical neurons with reciprocal corticocortical connectivity.

Among corticostriatal projection neurons, there is evidence that most direct path cells, but not most indirect path cells, are reciprocally connected over long ranges at the single unit level, and are a specialized population dedicated to intracortical connectivity and striatal innervation (“intratelencephalic”); the indirect path is predominantly innervated by collaterals of projections that descend through the pyramidal tract, and whose corticocortical collaterals are not reciprocal (Lei et al. 2004; Morishima and Kawaguchi 2006). As noted earlier, projections from interconnected cortical areas systematically converge on striatal FSIs at the single unit level (Ramanathan et al. 2002), and FSIs show a substantial preference for direct path SPNs (Gittis et al. 2010). Thus, the innervation of the direct path is distinguished by systematic patterns of reciprocal long range connectivity and corresponding striatal convergence, whereas the indirect path corticostriatal inputs are predominantly collaterals of descending fibers such as corticopontine motor output, whose cells of origin do not reciprocate with each other, and as reviewed below, show markedly less striatal convergence.

8.3. BG output to thalamus arises from activity in relatively superficial cortical layers, and passes exclusively through striatal matrix, while striosomes receive input from relatively deeper layers, with areal distinctions.

Evidence suggests that the direct path through the BG to thalamus implicates SPNs in the matrix compartment exclusively (Rajakumar et al. 1993), and that the corticostriatal innervation of the matrix is differentiated from that of the striosomes in important ways. While the striosomes and matrix are both broadly targeted by most cortical areas, the striosomes preferentially receive projections from L6 and deep L5, while the matrix is preferentially targeted by superficial L5, and by L2 and L3 (Gerfen 1989; Kincaid and Wilson 1996). Ascending projections from the densely direct-path-recipient PF thalamic nucleus pervasively and diffusely innervate the matrix compartment of associative striatum, while largely
avoiding striosomes; CM projections to sensorimotor striatum are less pervasive but similarly prefer matrix (Sadikot et al. 1992b). The CL and PC nuclei also project densely to the caudate striatum (Kaufman and Rosenquist 1985a). The striatal projections of these intralaminar nuclei appose the dendrites of SPNs, with varying physiological and morphological properties (Lacey et al. 2007), and evidence also suggests that they innervate striatal FSIs (Sidibé and Smith 1999). As proposed earlier, thalamostriatal projections may position the striatum to monitor (and therefore optimize and rapidly sequence) the synchronies that its output produces in thalamus, and thus presumptively in cortex, via BG output structures.

Intriguing areal distinctions in cortex have also been identified. In primate, dorsolateral PFC (DLPFC) targets matrix densely and broadly, largely avoiding striosomes, while orbitofrontal and anterior cingulate cortex preferentially target striosomes (Eben and Graybiel 1995). Matrix appears specialized to project to the pallidal segments and the SNr, while striosomes appear specialized to project to midbrain dopamine centers such as the substantia nigra compacta part (SNc), to whose densocellular zone they are reported to be reciprocally linked (Jiménez-Castellanos and Graybiel 1989; Crittenden et al. 2016).

Striosomes strongly influence the SNc and VTA through a pallidohabenular circuit (Rajakumar et al. 1993; Herkenham and Nauta 1979; Hikosaka 2010; Hong and Hikosaka 2008; Balcita-Pedíncio et al. 2011), while dopaminergic projections from the midbrain preferentially target striatal matrix (Graybiel et al. 1987). The involvement of striosome circuitry in motivational processing, and of dopamine in modulating responses to affective activity, is reviewed later. In particular, their roles in modulating the dynamics of superficial cortical microcircuits in PFC (Yang and Seamans 1996; Towers and Hestrin 2008), introduced earlier, are crucial.

### 8.4. Cholinergic, serotonergic, and dopaminergic localization to striatal matrix suggest specialization for dynamic, high fidelity processing of oscillatory signals.

The classic technique for differentiating striosomes from matrix is to stain the striatum to visualize distribution of the enzyme acetylcholinesterase (AChE) (Graybiel and Ragsdale 1978), rendering the striosomes as pale poorly stained patches. Serotonergic projections to striatum also preferentially innervate the matrix compartment (Lavoie and Parent 1990). As reviewed in detail later, dopamine, ACh, and serotonin are potent modulators of oscillatory neuronal responsiveness. Thus, differential prominence of these neurotransmitters in the matrix compartment suggests specialization for the relay of oscillatory activity.

Most striatal ACh arises from an intrinsic population of interneurons comprising 2-3% of striatal neurons (Contant et al. 1996), which is believed to be identical to the electrophysiologically identified tonically active neurons (TANs) of the striatum (Aosaki et al. 1995). These neurons discharge tonically at 2-10 Hz in the absence of sensorimotor activity, and are differentially localized to the matrix, particularly to the matrix border regions adjoining striosomes (Aosaki et al. 1995).

The PPN, itself profusely targeted by the GPi and SNr (Semba and Fibiger 1992; Grofova and Zhou 1998; Parent et al. 2001), provides an additional, extrinsic, supply of ACh to the striatum, and this too preferentially targets the matrix compartment (Wall et al. 2013). Moreover, the striatally projecting neurons of the midline and intralaminar thalamus are targeted by the PPN (Erro et al. 1999), and as noted earlier, preferentially target the TAN population, participating intimately in goal-directed learning (Bradfield et al. 2013). FSIs, noted above for their selective and robust innervation of direct path SPNs and their putative high fidelity relaying of oscillatory activity, are extensively modulated by cholinergic inputs (Koós and Tepper 2002). Thus, the matrix compartment of the striatum is distinguished by participation in multiple, coordinated cholinergic circuits.

### 8.5. A pattern of differential innervation in the direct path suggests specialization for integration and motivated action.

According to the BGMS model, the direct path of the BG establishes task-appropriate long range effective connections, while the indirect path largely serves to damp or desynchronize competing activity, to further secure the selected connections. Wall et al. (2013) identified instructive differences between afferents to these two intermingled populations of SPNs in mouse: The direct path was found to receive significantly heavier projections from primary somatosensory, ventral orbitofrontal, cingulate, frontal association, prelimbic, perirhinal, and entorhinal cortex, and to receive essentially the entire striatal projections from the amygdalar nuclei, STN, and DRN. The indirect path was found to receive a significantly heavier projection from primary motor cortex. Preferential targeting of the direct path by primary somatosensory, and of indirect path by primary motor, comports with a model in which the direct path establishes connections and facilitates actions consistent with context and task requirements, while the indirect path inhibits completed, competing, ineffective, and irrelevant activity and functional connectivity.

Direct path SPNs show higher activation thresholds and more extensive dendritic processes (~25% more dendrites) than indirect path SPNs, suggesting greater integration through the direct path (Gertler et al. 2008). When synchronized cortical activity is confined to a single focus in primary motor cortex, the consequent striatal activation strongly prefers the indirect path (Berretta et al. 1997). This disparity is a natural consequence of the...
indirect path preference of the corticostriatal projection originating in primary motor cortex. It might also be explained in part by a preferential responsiveness in the direct path to conditions of multi-areal activity, congruent with the role proposed in the BGMS model in which it is implicated in the induction of selective synchronies between distant areas that necessarily already harbor activity.

8.6. Cortical inputs to the direct path appear to be an exquisitely context sensitive sparse code, with relatively high divergence-convergence.

The information borne by the intratelencephalic corticostriatal projection appears to be distinct from that borne by the corticostriatal collaterals of the corticopontine projection from the same area. Turner and DeLong (2000) showed that in primate primary motor activity, corticopontine neurons consistently show activity associated with movement execution and, particularly, the muscular contractile command stream, whereas activity in intratelencephalic neurons is often independent of muscle activity, is exquisitely context- and feature-dependent, and is usually confined to a particular aspect of current conditions (sensory context, movement preparation, or movement underway). They suggested that these patterns of direct path input to the striatum are a sparse code, of the sort demonstrated in temporal and visual cortex (Rolls and Tovee 1995; Vinje and Gallant 2000). Wright et al. (1999, 2001) showed in rat that intratelencephalic corticostriatal afferents from primary sensory areas have diffuse, convergent, and bilateral terminal patterns, implicitly raising opportunities for information integration. In contrast, they showed that corticopontine collateral input is ipsilateral, and preserves topographic specificity and organization, terminating in discrete varicosities without convergence, with thicker and faster axons. Moreover, they showed that the intratelencephalic and corticopontine projections enter the striatum almost at right angles to each other, which appears to further cultivate information integration.

Earlier studies identified the differential pattern of corticostriatal arborizations, finding that those of the intratelencephalic collaterals in the striatum are ~1.5 mm in diameter, with sporadic branching and varicosities, while the corticopontine collateral arborizations are dense, focused within a volume with longest dimension ~500 µm, and do not cross boundaries of adjacent striosomes (Cowan and Wilson 1994; Kincaid and Wilson 1996). In another investigation of the differences between intratelencephalic and corticopontine pyramidal neurons, it was found that the corticopontine projection originates chiefly in lower L5, while the intratelencephalic projection originates chiefly in upper L5 and in L3 (with L3 predominating slightly in sensory cortex), and that the striatal terminal boutons of the former are roughly twice the size of the terminals of the latter (Reiner et al. 2003). This also shows suggestive alignment with laminar preferences in corticocortical projections, such that indirect path afferents arise from the same population as feedback corticocortical projections, and direct path afferents from the feedforward population (Barone et al. 2000; Markov and Kennedy 2013). However, caution is in order interpreting this evidence for laminar preferences. Despite evidence that afferents to the direct path arise predominantly from the intratelencephalic corticostriatal projection, while indirect path afferents arise from the corticopontine projection, no significant laminar preferences were identified for the direct and indirect paths in the study by Wall et al. (2013) noted above.

8.7. The direct and indirect paths, and striatal matrix and patch compartments, are neither crisply distinct nor mutually exclusive.

Preferential projection by classes of corticostriatal neurons is a matter of tendencies, not rules. Intratelencephalic corticostriatal axons prefer direct path SPNs by a 4:1 ratio, while corticopontine collateral axons prefer indirect path SPNs by a 2.5:1 ratio (Lei et al. 2004). Recent findings using genetically manipulated mice have shown that the cytological and hodological compartmentation of the striatum into striosomes and matrix is not crisp, with both striosomal and matriceal SPNs receiving both limbic and sensorimotor inputs, and projections to SNc arising from both striosomal and matriceal SPNs (Smith et al. 2016). Earlier studies demonstrated similar minor projections of sensorimotor cortex to striosomes, and revealed sparse projections from striosomal neurons to the pallidal segments (Flaherty and Graybiel 1993).

The canonical marker for direct and indirect path SPNs is expression of dopamine receptors from the D₁ and D₂ receptor families, respectively (Gerfen and Surmeier 2011), but SPNs express DA receptors from the opposing family at low levels (Smith and Kieval 2000), and BG microcircuits intermingle the effects of DA receptors from both families (Gerfen and Surmeier 2011). Indeed, the axons of individual SPNs in primate frequently branch to both direct and indirect path targets (Parent et al. 1995; Levesque and Parent 2005). Moreover, in the ventral pallidum, neurons with projection patterns characteristic of the Gpi/SNr and the GPe are closely intermingled, receiving projections from direct and indirect path SPNs (Groenewegen et al. 1993; Smith and Kieval 2000).

Voluntary behavior is preceded by simultaneous activation of both direct and indirect path SPNs (Cui et al. 2013). This coactivation, while typically antagonistic, is not symmetric (Oldenburg and Sabatini 2015). These dynamics are consistent with the proposition that “matriosomes” consisting of closely intermingled direct and indirect path SPNs, with presumptively overlapping
dendritic processes, facilitate coordination of direct and indirect path output (Flaherty and Graybiel 1993).

One obvious consequence of these various cross-channel and cross-receptor paths is that a wider pool of information is available to the implicated individual neurons, which they might use for contextualization and coordination.

9. Dopaminergic Regulation of Oscillatory Responses

In this section:

9.1. Dopamine intrinsic to the basal ganglia underlies prominent regulation mechanisms in and beyond the BG.
9.2. Dopamine communicates cognitive and motivational significance.
9.3. Dopamine in prefrontal cortex and associative thalamus augments responsiveness to afferent activity.
9.4. Dopamine promotes oscillatory synchronisation in and between the BG and motor cortex.
9.5. Dopamine promotes synchrony between the medial temporal lobe and prefrontal cortex, and stabilization of synchrony-mediated functional connectivity, promoting continuation and memorisation of effective behaviors.

9.1. Dopamine intrinsic to the basal ganglia underlies prominent regulation mechanisms in and beyond the BG.

Dopamine (DA) is a key modulatory neurotransmitter intrinsic to the BG, where it raises the excitability of direct path SPNs by activating their D1-class receptors, and attenuates the excitability of indirect path SPNs by activating their D2-class receptors (Gerfen and Surmeier 2011). The BGMS model is chiefly concerned with the influence of the BG on corticocortical circuit dynamics, so I do not undertake a thorough treatment here of the DA circuitry internal to the BG, or of the multifarious role posited for DA in the intrinsic dynamical control and reinforcement learning mechanisms of the BG. For reviews, see for example Schultz (1998), Bromberg-Martin et al. (2010), and Yetnikoff et al. (2014). Nonetheless, roles for DA in the control of oscillatory activity, in and beyond the BG, have been described that bear directly on the BGMS model.

9.2. Dopamine communicates cognitive and motivational significance.

The effects of DA are complex. Through broad projections to BG nuclei, frontal cortex, and associated thalamic nuclei, the release of DA arising from BG-controlled neurons in the ventral midbrain (chiefly SNc, VTA, and the retrorubral field, RRF) and other areas has been proposed to have a crucial role in motivational control, by signaling reward, surprise, novelty, even aversiveness, and in general, saliency (Bromberg-Martin et al. 2010). DA release has been proposed to signal the expected value of work, in order to encourage continuation of efforts expected to culminate in a rewarding outcome, and discourage continuation of other efforts (Hamid et al. 2015). Indeed this neuroeconomic function has been ascribed to the BG as an ensemble (Goldberg and Bergman 2011). As noted earlier, striosomes appear specialized to control ventral midbrain DA centers; medial PFC control of striosomes, and striosomal control of ventral midbrain DA, have been implicated in cost-benefit decision making (Friedman et al. 2015; Crittenden et al. 2016). DA also appears to be used to signal disparities between expected and actual outcomes, dipping phasically upon disappointment and rising phasically upon surprising reward, driving reinforcement learning mechanisms (Schultz 1998, 2013). In fact, evidence suggests that DA is crucial in signaling prediction errors per se, with or without reward associations (Sharpe et al. 2017).

Surprising sensory events can evoke prominent, short-latency DA bursts, regardless of reward association, in 60-90% of DA neurons throughout the full extent of the SNc and VTA, apparently constituting an alerting response serving to marshal attention; these bursts seem to correlate with the degree to which the stimulus captures attention by surprise, they diminish with predictability and familiarity, and they are fairly nonselective, triggered by sensory surprises that superficially resemble motivationally significant stimuli (Bromberg-Martin et al. 2010). This comports with the many studies that have found that the BG are integral to orientation of attention, and generation of responses, to motivationally relevant sensory stimuli (e.g. van Schouwenburg et al. 2010b; Cools et al. 2004; Leventhal et al. 2012).

9.3. Dopamine in prefrontal cortex and associative thalamus augments responsiveness to afferent activity.

In vitro studies on PFC pyramidal neurons have found that DA raises their excitability (Penit-Soria et al. 1987; Shi et al. 1997; Yang and Seamans 1996). Similarly, in the thalamic MD nucleus, DA acting through D2 receptors has been shown in vitro to raise sensitivity to afferent activity (Lavin and Grace 1998). DA release in the MD largely derives from direct appositions arising from the VTA;
Indeed neurons in the VA and VL nuclei are also directly targeted by the midbrain DA centers (VTA, SNC, and RRF), as are the midline nuclei (Sánchez-González et al. 2005). D2 receptors are found throughout the associative thalamus (Rieck et al. 2004), and while DA terminals only sparsely synapse on neurons in the intralaminar thalamus (Sánchez-González et al. 2005), D2 receptors in the CM, PF, PC, and CL nuclei are particularly dense (Rieck et al. 2004), suggesting a large role there for volume-conducted DA action, with correspondingly less spatiotemporal specificity.

### 9.4. Dopamine promotes oscillatory synchronization in and between the BG and motor cortex.

Following observations of treated and untreated parkinsonian primates, human and non-human, it has been proposed that DA has a decisive role in the regulation of global beta synchrony in BG, with increases in DA providing for narrowly focused striatal responses to cortical beta activity and consequent facilitation of action, while decreases in DA promote broad propagation of cortical beta, concomitant global beta synchrony, and the retarding or arresting of action (Jenkinson and Brown 2011; Magill et al. 2001). As noted earlier, the DA-depleted striatum is characterized by the spontaneous and pervasive formation of synchronized clusters of SPNs (Humphries et al. 2009).

A pattern of broad beta synchrony, focally disrupted in association with performance of rewarded tasks, has been found in healthy (non-parkinsonian) monkeys (Courtemanche et al. 2003). These patterns appear to be DA-dependent: In an experiment in which global DA levels were manipulated to ~500% and <0.2% of their natural baseline, the low-DA condition was accompanied by pervasive synchrony with locally prevailing LFP, while the high-DA condition showed widespread focal desynchronization from prevailing LFP in primary motor cortex and dorsolateral striatum (Costa et al. 2006). DA manipulation was not found to affect overall cortical firing rates, underscoring the primacy of synchrony (and not rate) in these dynamics. The pattern of the hyperdopaminergic condition resembles the “desynchronization” of focally synchronized gamma oscillations in activated thalamocortical ensembles (Steriade et al. 1996), which according to the BGMS model are often caused by synchronized oscillations propagating focally through the BG.

### 9.5. Dopamine promotes synchrony between the medial temporal lobe and prefrontal cortex, and stabilization of synchrony-mediated functional connectivity, promoting continuation and memorization of effective behaviors.

Injection of DA into PFC has been seen to induce a spontaneous increase in synchrony between PFC and hippocampal LFPs, and to starkly alter the dynamics of PFC pyramidal neurons; activity shifts from in-phase with reciprocally associated interneurons (suggesting interneuronal inhibition) to opposite phase (suggesting interneuronal augmentation) (Benchenane et al. 2010). These effects of DA injection on PFC-hippocampal synchrony and PFC pyramidal neuron dynamics mimicked those seen without DA injection, in a well-trained behavioral task (Y maze navigation), at the choice point (the fork). DA released upon well-predicted reward, by inducing synchronization of PFC-hippocampal cell assemblies, might assure that effective behaviors are committed to long term memory, while ineffective ones are not (Benchenane et al. 2011). Naturally, counterproductive behaviors must also be remembered as such, implicating DA release associated with general saliency (Bromberg-Martin et al. 2010).

As noted earlier, DA in PFC has been found to attenuate receptivity to inputs on L1 apical dendrites (Yang and Seamans 1996), and to depress GABAergic lateral interactions among L2/L3 interneurons (Towers and Hestrin 2008), reducing the spatiotemporal coherence of oscillation there. As DA level rises, PFC neurons may thus become progressively less affected by superficial inputs from the BG-recipient thalamus and corticocortical feedback paths, so that effective behaviors are protected from disruption and distractions, and in particular, from induction of empirically extraneous functional connectivity. Indeed, DA release in PFC is suggested to stabilize working memory items there (Gruber et al. 2006). The effect of DA release on cortex may extend well beyond directly DA-recipient frontal cortex: an integrative theory has been proposed by van Schouwenburg et al. (2010a) and Bloemendaal et al. (2015) that DA release in PFC induces it to influence interconnected posterior cortex to stabilize goal-relevant representations and protect them from distractions, even while DA release in the BG promotes flexible adaptive responses to new information.
10. **Acetylcholine, Serotonin, and the Thalamic Reticular Nucleus in Oscillatory Regulation**

In this section:

10.1. The basal ganglia influence central neurotransmitter sources in the brainstem and basal forebrain, modulating thalamocortical activity.

10.2. Acetylcholine supply to cortex and thalamus is centralized and specific.

10.3. Acetylcholine promotes cortical responsiveness; cholinergic blockade in cortex drastically attenuates cortical activation, and when coupled with serotonergic blockade, resembles decortication.

10.4. Acetylcholine in cortex shows complex facilitatory effects, bearing some similarities to those of dopamine.

10.5. Acetylcholine promotes thalamic responsiveness and high frequency thalamocortical synchrony.

10.6. Acetylcholine has complex and often facilitatory effects in the BG.

10.7. The cholinergic centers are tightly integrated with BG circuitry.

10.8. Noradrenaline supply is centralized, and indiscriminately recruits attention and arousal.

10.9. Serotonin supply to BG, cortex, and thalamus is centralized.

10.10. Serotonin has facilitatory effects beyond those of dopamine and acetylcholine.

10.11. The dorsal and median raphe nuclei are multifariously coupled with the BG.

10.12. The cholinergic and serotonergic systems are tightly coupled.

10.13. Projections from the nucleus basalis and dorsal raphe nucleus reflect corticocortical connectivity.

10.14. Prefrontal control of cholinergic, serotonergic, and noradrenergic centers is extensive and orients attention.

10.15. The thalamic reticular nucleus is implicated in oscillatory regulation, and is under BG and PFC control.

### 10.1. The basal ganglia influence central neurotransmitter sources in the brainstem and basal forebrain, modulating thalamocortical activity.

Beyond their GABAergic projections to thalamic relay and association nuclei, and their dopaminergic projections to frontal cortex and associated nuclei of the thalamus, the BG are positioned to modulate cortical and thalamic activity through projections to the basal forebrain (particularly the nucleus basalis of Meynert, NBM), the pedunculopontine and laterodorsal tegmental nuclei (PPN and LDT), the dorsal and median raphe nuclei (DRN and MRN) at the pontine level of the brainstem, and the thalamic reticular nucleus.

Despite comprising less than one percent of neurons, cholinergic cells perform crucial roles in, and indeed beyond, the nervous system (Woolf and Butcher 2011). They are proposed to play a key role in orienting attention (Sarter and Bruno 1999), in induction of vigilance and fast sleep rhythms (Steriade 2004), in induction of plasticity (Rasmusson 2000), and in the formation of memories (Hasselmo 2006). Serotonin is implicated in regulation of sleep and wakefulness (Pace-Schott and Hobson 2002; Monti 2011), cognitive and behavioral flexibility (Clarke et al. 2006), and signaling of reward magnitude (Daw et al. 2002; Nakamura et al. 2008). The TRN has crucial roles in attention and oscillatory regulation (Pinault 2004), and is also crucially involved in sleep processes (Contreras et al. 1997). These roles of the ACh and 5-HT systems, and the TRN, are evidently closely related to each other and to the roles of DA. Indeed, the supplies of DA, ACh, and 5-HT, are closely coupled, as detailed below.

### 10.2. Acetylcholine supply to cortex and thalamus is centralized and specific.

The ACh supply for the cortex and thalamus arises from the basal forebrain, particularly the NBM, and from the PPN and LDT nuclei in the brainstem reticular activating system. Comprehensive direct cholinergic projections from the NBM to cerebral cortex (Mesulam et al. 1983; Mesulam 2004) are posited to modulate the predisposition of the targeted areas to robust afferent-driven oscillation, with fine spatiotemporal specificity (Muñoz and Rudy 2014). Each individual neuron in the NBM projects to a small single area of cortex confined to a diameter of 1-1.5 mm, prompting the proposal that the cholinergic population of the NBM is arranged to give arbitrary addressability of small areas of cortex, permitting activation of complex constellations subserving specific functions (Price and Stern 1983). The NBM's projection to TRN further positions it to exert a wide-ranging influence over corticothalamic activity (Levey et al. 1987).

The PPN and LDT have wide-ranging subcortical cholinergic projections, comprehensively innervating the thalamus, including its reticular nucleus (Hallanger et al. 1987; Satoh and Fibiger 1986; Steriade et al. 1988; Paré et al. 1988; Lavoie and Parent 1994). PPN targeting of the thalamus includes its primary sensory nuclei—the
dorsolateral geniculate (DLG), medial geniculate (MG), and the ventrobasal complex (ventral posterolateral (VPL) and ventral posteromedial (VPM)) (Hallanger et al. 1987). It additionally projects densely to the NBM and nearly all BG structures (Lavoie and Parent 1994).

Underscoring their functional significance, these cholinergic supply centers have prominent roles in disease processes. PPN lesions result in akinesia, and PPN degeneration is associated with PD (Pahapill and Lozano 2000). Alzheimer's disease is associated with attrition of the magnocellular cholinergic population in the NBM, typically to less than 30% of normal (Arendt et al. 1983). In Sz, the concentration of choline acetyltransferase in PPN and LDT is markedly lower than normal, while the concentration of nicotinamide-adenine dinucleotide phosphate (NADPH) diaphorase appears to be roughly twice normal (Karson et al. 1996; German et al. 1999). Indeed, systemic cholinergic abnormality may be a frequent correlate of Sz, and atypical antipsychotics such as clozapine and olanzapine have a high affinity for muscarinic receptors (Raedler et al. 2006; Scarr and Dean 2008).

10.3. Acetylcholine promotes cortical responsiveness; cholinergic blockade in cortex drastically attenuates cortical activation, and when coupled with serotonergic blockade, resembles decortication.

If the tonic supply of ACh to a cortical locus is interrupted, neurons there become dramatically less sensitive to their excitatory afferents, and correspondingly more prone to quiescent synchrony with their neighbors; ACh modulates the propensity of these neurons to track high frequency afferent oscillation and generate corresponding efferent oscillation, particularly in the beta and gamma bands (Rodriguez et al. 2004). Phasic increase in ACh supply to an area, when coupled with afferent activity, induces profound plasticity within tens of minutes, persistently elevating the propensity of the targeted area to synchronize with afferent high frequency oscillation and consequently desynchronize with neighboring quiescent oscillation (Rodriguez et al. 2004).

If the supply of ACh by NBM to cortex is blockaded, stimuli produce grossly attenuated and less coherent gamma. Most of the brainstem diffuse modulatory systems may act on cortex indirectly through the NBM ACh and raphe 5-HT systems; cortical electrocorticographic (ECoG) activation can be completely abolished by concurrent blockade of ACh and 5-HT (Dringenberg and Vanderwolf 1997, 1998). Rats subjected to this concurrent blockade, and exhibiting complete loss of ECoG activation, nonetheless engage in active locomotion, with normal posture and open eyes; however their behavior is disorganized and aimless like that of decorticated rats, including repeated, unhesitating walking plunges over precipices, and insensate behavior in swim-to-platform tests (Vanderwolf 1992).

10.4. Acetylcholine in cortex shows complex facilitatory effects, bearing some similarities to those of dopamine.

In cortex, ACh is modulatory, neither excitatory nor nonselectively disinhibitory; its presynaptic release does not by itself induce postsynaptic activity (Sillito and Kemp 1983). When coupled with excitatory afferent activity, ACh has a dramatic facilitatory effect on most cortical neurons, while maintaining or narrowing their respective receptive fields; tonic activity (discharges attributable to background afferent activity) is also reduced, so the overall effect is a marked increase in signal/noise ratio (Sillito and Kemp 1983). The effect of ACh on cortical interneurons is more diverse, with fast spiking inhibitory (FSI) interneurons in L5 hyperpolarized via muscarinic receptors, disinhibiting the L5 pyramidal neurons they target, while low threshold spiking (LTS) inhibitory interneurons are excited via nicotinic receptors, raising inhibitory output to their more superficial targets in L1-L3 (Xiang et al. 1998). Cholinergic hyperpolarization of cortical FSIs may relax the coincidence detection window for perisomatic inputs to pyramidal neurons (Pouille and Scanziani 2001), effectively increasing their receptive field, even while the direct effect of ACh on them is a narrowing of their receptive fields as described above. Moreover, the coherent lateral spread of oscillatory activity in L2/L3 (Tamás et al. 2000) may be depressed by ACh hyperpolarization of FSIs (as by DA (Towers and Hestrin 2008)), spatially focusing activity in cortex.

It has been shown in behaving rats that short latency ACh release, through effects mediated by a diversity of receptor types, is crucial to the generation and synchronization of performance-correlated oscillation in PFC ( Howe et al. 2017). In task trials in which the animal detected a sensory cue, significantly elevated PFC ACh levels were detected within 1.5 s of cue presentation, and remained elevated until reward delivery. Gamma oscillation in the same area, measured by LFP, was found to be significantly elevated, at ~90 Hz from ~200-400 ms after cue presentation, then at ~50 Hz from ~400-1300 ms after the cue. Local infusion of an M1 muscarinic antagonist attenuated these gamma responses in trials in which the animal detected the cue, and was associated with a trend toward more missed cues. Infusion of a nicotinic antagonist attenuated the initial high gamma response to detected cues, and similarly had no effect on oscillatory power in trials in which the animal missed the cue. Detected cues, but not missed cues, were associated with significant cross-frequency coupling of the 50 Hz gamma response, to local theta oscillation detected by LFP. This coupling was abolished by infusion of the M1 antagonist, and was attenuated by the nicotinic antagonist.
10.5. Acetylcholine promotes thalamic responsiveness and high frequency thalamocortical synchrony.

The effects of ACh on thalamic neurons have been found to be similar to those in cortex, facilitating responsiveness of excitatory neurons to afferent activity via M1 and M3 muscarinic receptors, as well as via nicotinic receptors, and having an opposite effect on inhibitory interneurons, where it induces hyperpolarization via M2 receptors, indirectly facilitating responsiveness (Parent and Descarries 2008; Steriade 2004). The cholinergic projection to PF (representing intralaminar nuclei) densely terminates in exclusively direct synapses (Parent and Descarries 2008), and PP宁/LDT stimulation in the anesthetized cat, causing cholinergic activation of the thalamus, produces sustained, synchronized high frequency oscillation in intralaminar neurons and reciprocally connected cortical neurons, resembling patterns seen in the waking and REM sleep states (Steriade et al. 1996).

The terminal pattern of the cholinergic projection to the dorsal lateral geniculate nucleus (DLG, representing primary sensory nuclei) is almost entirely extrasynaptic (Parent and Descarries 2008), and this relatively diffuse pattern is likely to have markedly less spatiotemporal specificity than synaptic paths, so the diffuse ACh innervation of DLG comports with the expectation (according to the “binding by synchrony” hypothesis, briefly discussed later) that modulatory inputs to early sensory areas are arranged to not disrupt the fine time structure of activity therein. ACh inputs to the TRN are both synaptic (Parent and Descarries 2008) and extrasynaptic (Pita-Almenar et al. 2014), and are reported to hyperpolarize TRN neurons through M2 muscarinic receptors, disinhibiting their targets in the thalamus (Steriade 2004; Lam and Sherman 2010).

10.6. Acetylcholine has complex and often facilitatory effects in the BG.

ACh has a variety of effects on striatum, through a variety of receptors: it can directly induce SPN depolarization and spontaneous firing, and in particular, facilitate the excitability of NMDA (glutamate) receptors on SPNs, while simultaneously reducing glutamate and GABA release; corticostriatal long term potentiation (LTP) in SPNs is also dependent on ACh activation of M1 muscarinic receptors (Calabresi et al. 1998, 2000). As noted earlier, when intrinsic cholinergic interneurons in the striatum are subjected to synchronous spike volleyes, their cholinergic action on dopaminergic axons promotes intrinsic DA release in the striatum (Threlfell et al. 2012).

Early experiments entailing injection of cholinergic agents into striatum, pallidal segments, and STN, showed dysregulatory effects that generally appeared to be pathological activations (DeLong and Georgopoulos 2011).

10.7. The cholinergic centers are tightly integrated with BG circuitry.

It has been proposed that the PPN is so intimate with the BG as to constitute an inextricable component thereof (Mena-Segovia et al. 2004). The GPI, VP, and SNr strongly and systematically project high velocity axon collaterals to it (Semba and Fibiger 1992; Grofova and Zhou 1998; Haber et al. 1985; Parent et al. 2001; Harnois and Filion 1982), and cholinergic and glutamatergic cells in the PPN in turn profusely target dopaminergic cells in the SNc, with at least some of the PPN cells that target SNc receiving projections from SNr (Grofova and Zhou 1998). However, BG regulation of the PPN cholinergic supply to thalamus is complex, apparently largely indirect, and yet to be fully elucidated. BG projections to PPN have been reported to preferentially target non-cholinergic cells (Mena-Segovia and Bolam 2009), and the BG may reciprocate preferentially with the rostral sector of the PPN, while it is the caudal PPN that projects to the thalamus and tectum (Martinez-Gonzalez et al. 2011). However, it has also been reported that the GPI projects throughout PPN, most prominently to the central PPN (Shink et al. 1997), which in turn projects to the NBM (Lavoie and Parent 1994). Moreover, caudal PPN is targeted by the DRN, which itself is targeted by the BG, though the effect of 5-HT on the PPN is complex and unresolved (Vertes 1991; Steininger et al. 1997; Martinez-Gonzalez et al. 2011).

The ventral striatum projects profusely to all sectors of the NBM (Mesulam and Mufson 1984; Grove et al. 1986; Haber et al. 1990; Haber 1987), and the NBM receives substantial projections from the SNc and VTA, targeting cholinergic neurons (Zaborszky and Cullinan 1996; Gaykema and Zaborszky 1997). At least some VS afferents to NBM terminate directly on corticopetal cholinergic neurons; GABA input to these neurons is posited to dampen excitability, resulting in corresponding inattention in their cortical targets (Sarter and Bruno 1999). The GPe, like the NBM, but much less profusely, has direct cholinergic projections to cerebral cortex (Eid and Parent 2015), and both coexpress GABA in these projections (Saunders et al. 2015a, 2015b). And the GPe, like the NBM, projects directly to the TRN. The NBM may be an inextricable component of an extended BG system, as has been suggested of other areas of the substantia innominata (Heimer et al. 1997). Indeed a model has been proposed that integrates ACh projections from the NBM, the GPe, and the VP, with BG loop circuitry (Zaborszky et al. 1991, Fig. 6).
10.8. Noradrenaline supply is centralized, and indiscriminately recruits attention and arousal.

Noradrenaline (NA) originating in the locus coeruleus (LC) of the pontine tegmentum is implicated in the direct modulation of arousal throughout the forebrain; the LC responds to noxious, novel, and other highly salient stimuli, toward which attention is to be oriented, with low latency phasic responses time-locked to the stimulus (Berridge 2008; Sara and Bouret 2012). These phasic responses are posited to reset network connectivity to facilitate assembly of a new network oriented to the salient stimulus, and there is evidence that NA arising from LC has a more general role in set shifting, crucially implicating the reciprocal connectivity of LC with PFC (Sara and Bouret 2012).

However, the striatum is not an LC target (Aston-Jones and Cohen 2005), and descending inputs to the LC have been found to be highly restricted, excluding most BG and all thalamic structures; activation of LC by afferent activity has been found to be either generalized to its entirety, or generalized to an entire sensory domain; perhaps most tellingly, output from the LC has been found to be non-specific, with efferent populations in LC distributed throughout its extent, and only modest and partial segregation according to target structure (neocortex, thalamus, cerebellum, etc.) (Aston-Jones et al. 1986; Waterhouse et al. 1993; Loughlin et al. 1986).

Thus, while the LC is integral to the regulation of oscillatory activity and functional connectivity in the thalamocortical system, it seems clear that the LC is non-specific in its mechanisms. It also seems clear that it is not substantially integrated into BG circuitry, notwithstanding a sparse projection from the ventral pallidum to rostral LC (Groenewegen et al. 1993). It seems likely that stimulus-related network formation facilitated by LC reset signals entails broad synchronies to which the striatum responds after the fact.

10.9. Serotonin supply to BG, cortex, and thalamus is centralized.

5-HT supply to the telencephalon arises from the MRN and DRN, which project strongly to the midline, intralaminar, and mediodorsal thalamic nuclei, much of the BG, and to the entirety of cerebral cortex and the medial temporal lobe (Lavoie and Parent 1990; Vertes 1991; Vertes et al. 1999; Baumgarten and Grozdanovic 2000). Raphe projections exhibit complex specificity, with the DRN projecting to cortex with various topographies, while the MRN projects to cortex more diffusely (Wilson and Molliver 1991).

10.10. Serotonin has facilitatory effects beyond those of dopamine and acetylcholine.

5-HT has an effect on its cortical targets much like that of ACh, facilitating responses to afferents, yielding ECoG desynchronization (Neuman and Zebrowska 1992), though the effect on individual neurons is complex, with most cells depolarized via 5-HT₂ receptors but some hyperpolarized via other receptors (Davies et al. 1987).

5-HT₂A receptors are present on the apical dendrites of L5 pyramidal neurons, so 5-HT release facilitates responsiveness (Carter et al. 2005) precisely where it is inhibited by DA and ACh release. This effect apparently counteracts the posited focusing and stabilizing effects of DA and ACh described above; indeed almost all known hallucinogenic drugs act through this channel, and activation of 5-HT₂A receptors is necessary and sufficient for their hallucinogenic effects (Glennon et al. 1984; González-Maeso et al. 2007; Fiorella et al. 1995; but see Maqueda et al. 2015). The notion arising from the BGMS model is that 5-HT₂A agonists (even including, rarely, SSRIs for treatment of never-before-hallucinating patients (Bourkeos et al. 1998; Waltreit et al. 2013)) open cortical columns to induction of effective connections via spike-timing-dependent gain control by corticocortical feedback and BG-thalamocortical output, and hallucinogens thereby induce spurious information flow and associations that would not normally reach the implicated pyramidal somata.

These spurious have much in common with those associated with Sz; though the disconnection of Sz may principally or frequently be rooted in GABAergic and dopaminergic dysfunction (noted above), there is also a suggestion of 5-HT dysfunction (Geyer and Vollenweider 2008), and atypical antipsychotics such as clozapine, risperidone, and olanzapine show much higher affinity for 5-HT₂ receptors, which they usually occupy almost completely, than for the D₂ receptors targeted by earlier antipsychotics such as haloperidol (Kapur et al. 1999). Beyond this, common direct BG involvement is plausible. 5-HT₂C receptors in the striatum, activated by hallucinogens (Fiorella et al. 1995), have been found to excite striatal FSIs (Blomeley and Bracci 2009), and direct striatal involvement in Sz has been posited (Graybiel 1997; Simpson et al. 2010; Wang et al. 2015).

10.11. The dorsal and median raphe nuclei are multifariously coupled with the BG.

All parts of the BG are innervated serotonergically by the raphe nuclei, with heterogeneous density within and between the organs of the BG, and highest density in the SN and GP (Lavoie and Parent 1990). The median and dorsal raphe nuclei (MRN and DRN) are targeted by the VP and SNr (Peyron et al. 1997; Gervasoni et al. 2000;
Levine and Jacobs 1992; Groenewegen et al. 1993). Coupling with BG DA centers and DA control structures is extensive. The VTA projects to the DRN and MRN; the DRN and MRN also project to DA cells in the SNC and VTA, and raphe projections to the SNr appear to be directed to the dendrites of DA neurons (Baumgarten and Grozdanovic 2000). The lateral habenula (LHb) projects strongly to all parts of the DRN (Peyron et al. 1997) and to the MRN (Herkenham and Nauta 1979). The LHb is integral to BG DA circuitry – it is reciprocally linked with the VTA, directly and via the rostromedial tegmental nucleus (RMTg) (Herkenham and Nauta 1979; Hikosaka 2010; Balcita-Pedicone et al. 2011), and is profusely innervated by Gpi and VP (Parent et al. 2001; Hong and Hikosaka 2008; Shabel et al. 2012; Groenewegen et al. 1993).

10.12. The cholinergic and serotonergic systems are tightly coupled.

The MRN and DRN project densely to the PPN and LDT, and the DRN projects densely to the substantia innominata (including NBM, in primates) (Vertes 1991; Vertes et al. 1999; Steininger et al. 1997). The substantia innominata in turn projects to the DRN (Peyron et al. 1997), and PPN and LDT project to MRN and DRN (Semba and Fibiger 1992). The central 5-HT and ACh systems are thus directly and reciprocally coupled.

10.13. Projections from the nucleus basalis and dorsal raphe nucleus reflect corticocortical connectivity.

The NBM shows topographic organization such that single loci project jointly and specifically to interconnected areas of cortex, particularly frontal and posterior areas (Pearson et al. 1983; Ghashghaei and Barbas 2001; Zábovszyk et al. 2015). These areas of overlap (joint projection) in the NBM appear to entail distinct intermingled populations, with only a tiny minority (~3%) of cells collateralizing to both frontal and posterior areas (Zábovszyk et al. 2015), suggesting combinatorial flexibility. The raphe nuclei, particularly the DRN, are reported to exhibit similar organization, with small groups of dorsal raphe cells projecting to widely distributed, anatomically interconnected neocortical foci (Wilson and Molliver 1991; Molliver 1987). These arrangements in the basolocortical and raphe corticopetal projections reverse the corticostriatial convergence, noted earlier, of interconnected cortical regions.

10.14. Prefrontal control of cholinergic, serotonergic, and noradrenergic centers is extensive and orients attention.

Direct and dense projections from PFC and other frontal cortical association areas to the NBM (Mesulam and Mufson 1984), PPN, and LDT (Semba and Fibiger 1992) thence to cortex and thalamus is a putative mechanism for sustained attention and inattention (Sarter et al. 2001; Zábovszyk et al. 1997). Indeed, PFC inactivation completely abolishes sensory-evoked ACh release in the sensory thalamus, and significantly reduces tonic ACh release in sensory cortex (Rasmusson et al. 2007). PFC projections to the DRN (Gonçalves et al. 2009) and LC (Jodoj et al. 1998; Aston-Jones and Cohen 2005) are thought to have similar and related functions. Because PFC is thoroughly and densely targeted by BG output via the thalamus and the midbrain DA centers, and projects directly and strongly to all BG input structures, PFC control of cholinergic and serotonergic centers implies BG influence on them, and suggests further coordination of output from these modulatory centers with BG output.

10.15. The thalamic reticular nucleus is implicated in oscillatory regulation, and is under BG and PFC control.

The TRN, through GABAergic projections to other thalamic nuclei, is thought to act in a modulatory role, influencing activity and oscillations in the entire thalamus and cortex, particularly corticocortical functional connectivity (Pinault 2004). A crucial role in the generation of spindles during sleep is recognized (Contreras et al. 1997). Prefrontal projections to TRN are thought to play a prominent role in orientation of attention and suppression of distractors (Zikopoulos and Barbas 2006; Guillery et al. 1998), and dysfunction of the TRN, resulting in deficits in these and related functions, has been associated with Sz (Ferrarelli and Tononi 2011; Pinault 2011). The GPe projects to the full rostrocaudal extent of the TRN (Hazrati and Parent 1991; Shammah-Lagnado et al. 1996), and BG inputs to the TRN target cells that project to the intralaminar thalamus (Kayahara and Nakano 1998). Experiments in vitro suggest that DA release in GPe inhibits its inputs to TRN (Gasca-Martinez et al. 2010). Excitatory, glutamatergic nigroreticular projections have been demonstrated arising from striatum-recipent cells throughout the SN, both from the pars reticulata and the pars compacta, with roughly half of these fibers also found to release DA (Antal et al. 2014).

The interposition of the thalamic reticular nucleus in collaterals of L6 corticothalamic projections (Deschénes et al. 1994) is posited to produce nonlinearity, such that low frequency activity has a suppressive influence on thalamus via the TRN, while higher frequency activity is stimulative (Crandall et al. 2015). Modulation of the TRN (by the BG and PFC, in particular) might alter this dynamic, providing for adjustment of the threshold above which cortical activity stimulates activity in BG-recipient thalamus, and below which it is suppressive. This would gate the action of the BG on cortex, by controlling the supply of activity available for modulation at the implicated thalamocortical neurons. The BG and PFC are arranged to control this gate
by adjusting the ACh supply to TRN, reducing or abolishing the suppressive influence of the TRN on corticothalamic targets (Lam and Sherman 2010).

11. Basal Ganglia Involvement in Sensory Processing

In this section:

11.1. The basal ganglia make selections in the sensory domains.
11.2. Basal ganglia influence on primary sensory thalamus is modulatory, not entraining or resetting.
11.3. The basal ganglia project widely to sensory cortex, with notable exceptions.
11.4. Basal ganglia output beyond the direct path projects to sensory areas at the cortical, thalamic, and brainstem levels.
11.5. The basal ganglia may mediate attentional neglect of percepts arising predictably from intentional acts by the self.

11.1. The basal ganglia make selections in the sensory domains.

The BG have been proposed to function in perceptual decision making in a fashion analogous to their function in behavioral decision making (Ding and Gold 2013). As reviewed earlier, BG direct path output is arranged to influence activity not only in frontal cortex, but in posterior areas, including posterior sensory areas. Motor control, long associated with the BG, has an inherent intimacy with attention, which entails selective perception; for example, common mechanisms and networks have been identified underlying attention and oculomotor control, both within and beyond the BG (Corbetta et al. 1998; Hikosaka et al. 2000). Attention is accompanied by significant and performance-correlated upward shifts in the power spectrum of activity in the BG-recipient central thalamus (Schiff et al. 2013). Pathways described earlier by which the BG modulate central DA, ACh, and 5-HT supplies, and the TRN, imply a broad modulatory influence of the BG on sensory processing.

11.2. Basal ganglia influence on primary sensory thalamus is modulatory, not entraining or resetting.

Primary sensory areas of the thalamus, and thalamic sensory areas in intimate topographic registration with the primary areas, are apparently avoided by direct path output (Percheron et al. 1996; Parent et al. 2001). This arrangement is an expected corollary of the proposed “binding by synchrony” mechanism (von der Malsburg 1999; Singer and Gray 1995; Womelsdorf et al. 2007; Jia et al. 2013; Barth and MacDonald 1996; Siegel et al. 2008). Rigid BG-induced spike timing disruption of sensory processing pipelines at the thalamic level would derange the spatiotemporally precise registration by which ensembles of neurons representing a stimulus are proposed to be coherently bound together, and to be differentiated from neurons in the same area that are active but not associated with the stimulus. In fact, there is evidence for binding by synchrony in sensory nuclei of the thalamus; corticothalamic projections bearing synchronized oscillations associated with a visual stimulus entrain thalamocortical activity associated with that stimulus, increasing the effective neuronal gain for associated features (Sillito et al. 1994).

11.3. The basal ganglia project widely to sensory cortex, with notable exceptions.

While the BG direct path output apparently avoids sensory thalamic nuclei, it does not avoid sensory areas at the cortical level. As noted earlier, the BG-recipient intralaminar nuclei (CL, PC, CM, and PF) have been shown to project to visual, auditory, and somatosensory cortex (Van der Werf et al. 2002; Scannell 1999), and the MD, VA, and VL nuclei have been shown in primates to project to visual association cortex and the angular gyrus area of parietal cortex (Middleton and Strick 1996; Clower et al. 2005; Tigges et al. 1983). In the rostral intralaminar thalamus, the PC and CL nuclei show distinct intimacy with sensory areas, reaching all visual areas but the primary receptive fields; these projections show no apparent topographic pattern, but are accompanied by heavy projections to densely interconnected areas such as the frontal eye fields and posterior parietal association areas 5 and 7, with some axons found to collateralize multi-areally, e.g. to visual area 20a and areas 5 and 7 (Kaufman and Rosenquist 1985a; Van der Werf et al. 2002).

As noted earlier, the caudal intralaminar nuclei in cat project to secondary and some associative auditory cortex, but avoid the primary, posterior, ventroposterior, and temporal auditory fields (Scannell 1999). This extensive lacuna suggests that the early stages of auditory processing are particularly sensitive to disruption of spike patterns. This might be attributable to the unique orientation of
auditory perception to environmental phenomena (sounds) that are typically oscillatory and momentary, so that the crucial phenomenological attributes of stimuli can only be represented in early processing stages with neural spikes that are precisely locked in time to occurrence of those attributes.

11.4. Basal ganglia output beyond the direct path projects to sensory areas at the cortical, thalamic, and brainstem levels.

The projection systems associated with the GPe, SN pars lateralis (SNi), PPN, LDT, NBM, and DRN extensively target sensory areas, including those in thalamus. As noted above, the PPN targets the primary sensory nuclei of the thalamus (Hallanger et al. 1987). The caudal GPe projects directly to the auditory and visual sensory sectors of the caudal TRN, to auditory cortex, the inferior colliculus, and through the SNi further influences visual and auditory processing via the latter's projections to the superior and inferior colliculi (Shammah-Lagnado et al. 1996; Moriizumi and Hattori 1991; Yasui et al. 1991). Projections of GABAergic cells in the NBM to TRN target the vision-specific portion of the latter, while cholinergic cells in NBM project to corresponding visual cortex (Bickford et al. 1994). While paths through the DRN from BG output structures to sensory cortex have yet to be directly demonstrated, the DRN comprehensively innervates cortex (Vertes 1991) and, as reviewed earlier, is reciprocally coupled to the BG.

The superior colliculus is a key center for sensory (particularly visuospatial) processing: it is implicated not only in ocular saccades but in covert (i.e., non-motoric) orienting of attention (Robinson and Kertzman 1995), supplies powerful inputs to thalamic MD and pulvinar nuclei (Wurtz et al. 2005) thence to visuocognitive cortex (Berman and Wurtz 2010; Lyon et al. 2010), and is under the direct influence of the SNr (Hikosaka and Wurtz 1983). It is quite intriguing that BG output avoids the pulvinar, but extensively innervates the SC, given that the SC extensively innervates the pulvinar. Perhaps this relates to the proposed imperative to avoid deranging fine timing information in thalamocortical sensory modules. Nigrocollicular terminals, while GABAergic, mostly appose medium or small dendrites (Behan et al. 1987); enveloping perisomatic GABAergic appositions like those of the nigrothalamic projection (Bodor et al. 2008) are present in the same tectal population, but arise elsewhere (Behan et al. 1987).

11.5. The basal ganglia may mediate attentional neglect of percepts arising predictably from intentional acts by the self.

The paths through the dorsal striatum to GPe, thence to TRN and thalamus, from the SNr to the SC, thence to thalamus, and from the ventral striatum to NBM, thence to cortex, may be crucial elements of a system that continually transforms behavioral output into selective, anticipatory inattention.

Corticostrial input from primary motor cortex has been found to preferentially flow to the GPe (Wall et al. 2013), and corticostrial input flowing to GPe is predominantly collaterals of axons destined for the pyramidal tract, bearing activity tightly correlated with executed motor commands (Lei et al. 2004; Morishima and Kawaguchi 2006). Collaterals of these axons also target the proximal dendrites of projection neurons in the intralaminar thalamic nuclei (Deschênes et al. 1998), from which these signals are relayed to all components of the BG. A key role posited for the signals carried by collaterals of motor output is as an “efference copy” or “corollary discharge”, primarily serving to contextualize sensory input, as suggested by projections from motor cortex to somatosensory cortex (DeFelipe et al. 1986). These signals may also serve to inform a system that differentiates between self-generated and other-generated percepts, attending the latter while disregarding the former (Crapse and Sommer 2008).

The BG might continually compute a dynamic template imparted upon the thalamus via the TRN and SC, and upon the cortex via the NBM, so that sensory input that is the expected result of motor output, and is therefore cognitively extraneous and distracting, is functionally disconnected. Sparsity in direct path corticostrial input, but not in indirect path input (Turner and DeLong 2000), comports with particular involvement of the indirect path in mediating this continual expectation-driven inattention. GPe facilitation of the TRN might act particularly by raising the threshold for corticothalamic inputs to transition from inhibitory to excitatory effects on their thalamic targets (Crandall et al. 2015). The BG influence the SC directly (Hikosaka and Wurtz 1983), and if an effect of this influence is to induce neglect of expected percepts, then unexpected percepts will be salient. This comports with evidence that the SC, upon encountering unexpected sensory events, can reconfigure sensorimotor orientation in the thalamus via the zona incerta (Watson et al. 2015). The combined dynamic suggests the BG learn to minimize surprise, centrally implicating dopamine signaling (Schultz 1998, 2013), as noted earlier. Indeed, some highly abstract models of cognition imply that the minimization of surprise is an organizing principle for the brain as a whole (Friston 2010).

It has also been suggested that BG-mediated selection of an action jointly activates areas implicated in processing the expected perceptual correlates of that action (Colder 2015; but see Urbain and Deschênes 2007). The combined dynamic might consist of activation and effective connection of the executive and perceptual areas implicated in the action, culminating in execution of the action, whereupon an efference copy of the corticofugal
motor output follows the paths through the BG to the TRN and NBM described here, in addition to corticocortical paths. By this narrative, if the action has the expected result, TRN and NBM outputs mask out the associated sensory inputs, presumably with a crucial role for collaterals of motor cortex output projecting to somatosensory areas of cortex and thalamus. If the results of the action deviate from expectations, then sensory inputs associated with the deviation are not masked out, but act as bottom-up drivers with particular salience due to the anticipatory recruitment of the associated cortical perceptual areas. The disparity is thus efficiently signaled, facilitating remediation.

That the BG systematically adjust sensory perceptions to track expectations and minimize surprise is suggested by the finding that the ventral striatum and ventral pallidum mediate prepulse inhibition of the acoustic startle response (mild auditory stimulus presented 30-500ms before startling stimulus) (Kodsi and Swerdlow 1995). This prepulse inhibition is deficient in many diseases associated with the BG, including OCD, Huntington's disease, and GTS (Swerdlow and Geyer 1998), is attenuated in Sz (Swerdlow and Geyer 1998; Quednow et al. 2008; Geyer and Vollenweider 2008), and is altered by hallucinogenic drugs (Vollenweider et al. 2007; Geyer and Vollenweider 2008).

There is evidence that corollary discharge underlying self-other differentiation is generally dysfunctional in Sz (Ford et al. 2001). Even basic coordination of motor output with sensory input is affected: smooth tracking of moving objects with the eyes is consistently impaired in Sz patients and their close relatives (Levy et al. 1994). This might be explained by dysfunction of the mechanisms of anticipatory inattention, if internally caused and therefore predictable sensory events are given spurious salience, prompting inappropriate actions (e.g., saccades). Deficient performance in Sz on stimulus-antisaccade tasks might be similarly rooted in dysfunction of the mechanisms of executive inhibition (Fukushima et al. 1988).

The accurate differentiation of self-generated from other-generated effects is crucial in the cognitive representation of agency (intentionality), and its dysfunction is likely intrinsic to Sz (van der Weiden et al. 2007). Evidence of projections in higher primates from the MD, VA, and VL nuclei to the angular gyrus (Tigges et al. 1983) is also suggestive, as this cortical area has been shown in humans to have a role in awareness of action consequences, and in particular, in the detection of disparities between intentions and results (Farrer et al. 2008), suggesting extensive BG involvement in the dynamics of agency. Agency in itself seems to influence the perception of results relative to the actions that produced them: Subjective intentionality significantly shortens the reported delay between action and results, compared to delays reported in involuntary action scenarios (such as an experimenter tugging an appendage with a fabric loop), and this shortening is lessened when the sense of agency in the action is disrupted by hypnosis (Lush et al. 2017) or coercion (Caspar et al. 2016).

12. The Roles of the Basal Ganglia in General Cognitive Coordination

In this section:

12.1. The basal ganglia are implicated in the regulation of all large scale cortical networks.

12.2. The combinatorially prodigious demands of cortical coordination are met by the combinatorial power of the basal ganglia.

12.3. As controllers of corticocortical information routing, the BG are integral to higher mental function.

12.4. The basal ganglia are arranged to control chaotic dynamics in cortex.

12.5. The basal ganglia are positioned to serve a central role in mental supervision and problem solving.

12.6. The basal ganglia are intimately involved in the mechanisms of working memory.

12.7. Functional parcellation of frontal cortex and basal ganglia is complex, and may emphasize intrinsically persistent and preparatory activity in frontal cortex, and impulsive and reactive activity in basal ganglia.

12.1. The basal ganglia are implicated in the regulation of all large scale cortical networks.

The BGMS model implicates the BG in the activation and coordination of all large scale cortical networks, spanning and pervading the sensory, motor, cognitive, and motivational domains, and particularly involving effective connections that combine these domains. Evidently, general cognitive coordination is uniquely challenging in terms of combinatorial tractability. BG physiology reviewed earlier implies that they are suited for such a role; here I explore this proposition more directly and in greater depth.
12.2. The combinatorially prodigious demands of cortical coordination are met by the combinatorial power of the basal ganglia.

The connectedness of the cerebral cortex—the proportion of combinatorially possible direct long range links that are anatomically actualized—is quite high, at least 66% in macaques (Markov et al. 2014). 130-140 distinct cortical areas have been identified in the macaque (Markov et al. 2014), implying at least 5,500 (66% × (130 × 129) × ½) bidirectionally or unidirectionally interconnected pairs in each hemisphere and as many as 25,000 such pairs overall. More notionally, these figures imply at least $10^{78} (2^{130} \times 2)$ distinct areal combinations, some substantial fraction of which might be both anatomically connected and usefully selected for momentary multi-areal effective connectivity. In humans, the number of distinct cortical areas is even larger, estimated at 180 (Glasser et al. 2016), implying more than 40,000 linkages and $10^{108}$ distinct areal combinations. The sheer scale of this network is also apparent in the estimated populations, with roughly $8 \times 10^9$ neurons and $6.6 \times 10^{13}$ synapses in the human cortex, connected by roughly 10 million kilometers of axons (Murre and Sturdy 1995).

Implicit to the BGMS model is a proposal that the mammalian brain tames these combinatorial and population explosions with a mechanism combining spatiotemporally precise but mesoscopic connectivity selection with the stupendous topological flexibility of the BG. The corticostratial projection, with its prodigious convergence and divergence (Flaherty and Graybiel 1994; Hintiryan et al. 2016), a total synapse population in humans of roughly 1 trillion ($10^{12}$) (Kreczmanski et al. 2007; Kincaid et al. 1998; Zheng and Wilson 2002), and uncorrelated postsynaptic activity (Wilson 2013), is suited to play a key role. Moreover, the unusual diversity of conduction delays through the BG, reviewed earlier, may arrange for a population of “polychronous groups” of neurons that exceeds not only the number of neurons in the system, but perhaps even the number of synapses (Izhikevich 2006).

In this view, each projection neuron in the striatum transiently participates in a vast array of contextually activated assembles, each of which relates particular spatiotemporally dispersed inputs to corresponding learned spatiotemporally focused outputs, projecting to pallidal/nigral projection neurons, which in turn focally target the thalamus (and other areas). This arrangement is similar in some important respects to arrangements of massive phased arrays of independent antennas, used and proposed for transmission and reception of signals in extremely flexible, high capacity, parallel, dynamically configurable communication links (Rusek et al. 2013) and, particularly, radar systems (Fuhrmann et al. 2010).

12.3. As controllers of corticocortical information routing, the BG are integral to higher mental function.

It has been previously proposed that the BG act to control the routing of information within cortex, dynamically establishing bridges between “source” and “destination” regions to facilitate goal-directed cognition (Stocco et al. 2010), and that population-level synchronies are an effective mechanism for flexible, selective signal routing (Akam and Kullmann 2010). Open circuits through the BG and thalamus, originating in one region and projecting to another one distant from the first, have long been appreciated (Joel and Weiner 1994).

Within the global workspace model of cognition (Dehaene and Naccache 2001; Baars 2005; Dehaene and Changeux 2011; Baars et al. 2013), the BG might arbitrate ephemeral access to specialized processors, and more generally, “dynamically mobilize” cortical areas for effective connection within the long range distributed network of conscious cognition. Equivalently, in the dynamic core model (Tononi and Edelman 1998), the BG might determine from moment to moment which corticothalamic modules are functionally well-connected.

Hybrid metaheuristics, a combinatorial optimization technique, involves such arrangements (Blum et al. 2011); densely and broadly connected areas may comprise a generic problem-solving (metaheuristic) mechanism, while more specialized and less widely connected areas are selectively integrated with the generic mechanism, when their respective domains of expertise are relevant to problems for which conscious intervention has occurred. The BG figure prominently, because many of the cortical areas with the highest anatomical and functional connectedness—areas including the superior and lateral prefrontal, anterior cingulate, and medial orbitofrontal (Cole et al. 2010; van den Heuvel and Sporns 2011; Harriger et al. 2012; Elston 2000)—are particularly dense targets of BG output (Middleton and Strick 2002; Ullman 2006; Akkal et al. 2007). Indeed, the striatum itself has been found to contain the most connected brain regions by some measures (van den Heuvel and Sporns 2011).

Proponents of the global workspace theory of consciousness contemplate “auto-catalytic” organization of long range functional networks in cortex (Dehaene and Naccache 2001) to avoid a homuncular infinite regress (Dehaene and Changeux 2011). The BGMS model implies that these functional networks are self-organized by a coalition of cortical and subcortical mechanisms, with the BG in particular crucial to the selection and recruitment of cortical networks, and to the inhibition of areas not implicated in a selected network. The combined system of the PFC and BG has been proposed expressly to constitute a mechanistically complete explanation for coherent cognition, avoiding implications of a cognitive homunculus (Hazy et al. 2006). Curiously, the
sensorimotor striatum contains many fragmentary sensorimotor homunculi in various configurations (Flaherty and Graybiel 1994), implying that the associative striatum contains many fragmentary cognitive maps, which through the looping architecture of the BG, might be said to regress infinitely, and substantively so (see more below, regarding perturbative iteration).

12.4. The basal ganglia are arranged to control chaotic dynamics in cortex.

The arrangement of the BG to influence cortical activity mesoscopically, without driving activity directly, has inspired the view that they dynamically modulate state attractors, shaping the evolution of cortical activity (Djurfeldt et al. 2001). This view is particularly appealing in light of evidence that the cerebral cortex intrinsically balances excitation and inhibition, supporting continually evolving dynamical activity (van Vreeswijk and Sompolinsky 1996; Haider et al. 2006; Okun and Lampl 2008; but see Haider et al. 2012 regarding primary sensory cortex). A related view is that cortex in the awake but resting state exhibits critical dynamics, characterized by high dimensionality (prolific possibilities), while attention focused on a task induces broad subcriticality, reducing susceptibility to distractors (Fagerholm et al. 2015).

It has been proposed that consciousness in its essence is a series of selected states, each an ephemeral complex of informational relationships, within an internally well-connected system with massive dimensionality and the power to discriminate among the myriad possible states as wholes—in mammals, the system of the cerebral cortex and thalamus (Tononi 2004). The physical aspects of the brain directly implicated in consciousness are proposed to be those with maximal cause-effect power (Tononi et al. 2016). By these criteria, the global integration of cortical states implicit to the massive divergence and convergence of the BG, and predominant BG control of spiral patterns in many of their thalamocortical targets, signify a central role in consciousness. Indeed, network delays result in notionally infinite dimensionality (Izhikevich 2006), and as reviewed earlier, such delays are particularly pronounced and diverse in the BG.

12.5. The basal ganglia are positioned to serve a central role in mental supervision and problem solving.

Conscious cognition, and prefrontal cortex (itself integral to BG circuitry), are thought to be crucial for high level supervision, particularly the goal-motivated resolution of problems not resolved at lower (more local) levels (Dehaene and Naccache 2001; Miller and Cohen 2001). In particular, the anterior cingulate cortex (ACC) and DLPFC are thought to subserve detection and mitigation of conflicts, through an iterative looping arrangement (Carter and van Veen 2007). As noted above, these areas densely reciprocate with the BG, with the ACC particularly targeting striosomes (Eblen and Graybiel 1995). As a dense target of mesencephalic DA, ACC has been proposed to form a loop with the BG subserving conflict management (Holroyd and Coles 2002).

In terms of goal-motivated and iterative problem solving, a striking corollary of the BGMS model is that the BG both recognize and generate large scale patterns of synchrony in cortex, so that synchrony-oriented information processing in the BG is not just integrative, but recurrent. Iteration can provide for the formulation of solutions by a process of perturbative adjustments to representations (Loureno et al. 2003), constituting a metaheuristic algorithm. Structural and functional recurrence in the PFC and BG in particular have been suggested to arrange for the progressive integration of evidence to drive decisions (Bogacz and Gurney 2007; Caballero et al. 2016), and the dynamical emergence of valuations and decisions, with structural hierarchy and hidden layers enabling adaptation to varying timescales (Hunt and Hayden 2017).

Optimization without a priori expertise can benefit from random perturbations, whereby the system can escape from local optima to find global optima (Loureno et al. 2003). It is thus interesting that pallidal and nigral projection neurons appear to be arranged to continually inject noise into the thalamocortical system, through their tonic, rapid, independently rhythmic discharges. While this noise may improve signal fidelity in important respects, as suggested earlier, it may also act to randomly perturb BG-thalamocortical state, via thalamocortical, thalamostriatal, thalamopallidal/thalamonigral, and thalamospinthalamic projections. Until a representation is robustly stabilized, these random perturbations may contribute crucially to an organism’s search for useful responses to environmental challenges and opportunities.

12.6. The basal ganglia are intimately involved in the mechanisms of working memory.

Dopamine release in PFC is proposed to stabilize working memory (WM) items, represented as attractor networks, against distractors and noise, simultaneous with its release in the BG enhancing targeted output to those same cortical loci (Gruber et al. 2006). This proposal comports neatly with findings, discussed earlier, that dopamine increases overall PFC pyramidal neuron responsiveness to afferent activity, but reduces the responsiveness of their L1 apical dendrites (Yang and Seamans 1996), and depresses GABAergic lateral interactions in L2/L3 interneurons (Towers and Hestrin 2008). WM impairment in Sz has long been recognized as a cardinal symptom (Lee and Park 2005), and may be explained in large part by dysfunctions of DA regulation, excitatory-inhibitory balance, functional connectivity, and apical dendrite excitability (Uhlhaas 2013; van den Heuvel et al. 2013; Braver and Cohen 1999;
BG intimacy with the thalamic MD and VA nuclei underscores a multifarious role for the BG in managing working memory (Frank et al. 2001; McNab and Klingberg 2008; Chatham and Badre 2015; Kalivas et al. 2001; Haber and Calzavara 2009; Watanabe and Funahashi 2012; Mitchell and Chakraborty 2013; Xiao and Barbas 2004; Parnaudeau et al. 2013). In this view, the BG gate the establishment of items in WM and their inclusion in subsequent cognition, and eject them from WM when they are no longer relevant to current context and goals, enabling reallocation of WM resources. Recent results show that the densely BG-recipient MD nucleus in particular can operate in precisely this fashion, sustaining context-dependent WM-related activity in PFC during delay periods (Bolkan et al. 2017), and regulating rule-contingent functional connectivity in PFC (Schmitt et al. 2017).

Prefrontal gamma power increases as a function of WM load (Roux et al. 2012), and alignment of the fine phase angle of spikes in an oscillating cell subpopulation in PFC, relative to prevailing oscillation in the wider population, may serve to delimit and orthogonalize items represented by that subpopulation (Siegel et al. 2009). In an arrangement analogous to spike-timing-dependent selection among conflicting sensory inputs (Fries et al. 2002), BG-mediated selection among current working memory items might entail synchronization of thalamocortical spiking impinging on jointly targeted connectivity hubs, with the corticocortical spiking associated with the selected item. BG-facilitated gamma bursts, securing effective connections, may thereby be produced, reintegrating the WM item into ongoing cognition. Indeed, gamma bursts in PFC accompany (putatively, induce) both the establishment of items in WM, and the activation of those items for subsequent inclusion in ongoing cognition (Lundqvist et al. 2016).

While WM entails persistent activity (Curtis and D’Esposito 2003; Wang 2001; Goldman-Rakic 1995), WM items may be further stabilized by ephemeral synaptic potentiation and associated ephemeral attractor states in cortex (Lundqvist et al. 2016; Rose et al. 2016). Some models of PFC-BG function in WM in fact necessitate such an intracellular state maintenance mechanism (Frank et al. 2001).

12.7. Functional parcellation of frontal cortex and basal ganglia is complex, and may emphasize intrinsically persistent and preparatory activity in frontal cortex, and impulsive and reactive activity in basal ganglia.

It seems clear that the frontal cortex and the BG are functionally coextensive components of a single inextricable system (Frank et al. 2001; Miller and Cohen 2001; Calzavara et al. 2007; Miller and Buschman 2007). Their functional delineation is thus fraught with nuance and ambiguity. One interpretation is that the BG learn associations quickly, at a lower level of generality, and frontal cortex learns associations more slowly, at a higher level of generality and stability, trained by the BG, so that frontal cortex eventually takes the lead in responding to stimuli (Miller and Buschman 2007; Antzoulatos and Miller 2011). While it is intuitively obvious that representations reflecting a larger number of examples will tend to be more general and abstract, it is not clear that the BG and frontal cortex differ crucially on this count. Even after over-training of a task, at least in some scenarios activity in the BG still leads that in frontal cortex (Antzoulatos and Miller 2014), and there is strong evidence that at least in some forms of motor learning, cortex is critical for initial acquisition but not necessary for performance subsequent to consolidation (Kawai et al. 2015).

According to Frank et al. (2001), the frontal cortex represents information with persistent patterns of activation, while the BG fire selectively, usually impulsively, and only coincident with substantial afferent activity, to induce updates to those persistent patterns. The BGMS model comports with this view: in BGMS, the BG induce contextually appropriate shifts in effective connectivity in response to cortical patterns of activation. The BGMS model, and the model of Frank et al. (2001), comport with the sparse pattern of task-specific activity exhibited by direct path corticostriatal neurons (Turner and DeLong 2000), noted earlier, because the corticostriatal activation associated with a particular behavioral and environmental conjunction is thereby inherently spatiotemporally limited. Cortical inputs to the indirect path arise mainly from a different population (Wall et al. 2013) that is not at all sparse in its activation patterns, consistent with an inhibitory function.

There are hints to the functional delineation of frontal cortex and BG in the results of several fMRI studies. A study by Cools et al. (2004) arranged to separate the metabolic correlates of shifts in the task relevance of objects (effectively, polymodal sensory stimuli), from those of transiently operative abstract rules. The BG and PFC were both found to be integral to the former type of preparatory shift, allocating attention and responsiveness to the task-appropriate stimuli, but not to the latter, which was only associated with activity in PFC, subsequently biasing striatal responses appropriately. Another study showed activation of the BG when unexpected sensory stimuli prompted reorienting of attention, but not in preparatory orienting and maintenance of attention (Shulman et al. 2009). A similar study identified a role for the ventral BG in mediating shifts of preparatory attention in response to unattended (but evidently detected) sensory cues, inducing appropriate changes in frontal-posterior functional connectivity (van Schouwenburg et al. 2010b).
Exploration of the physiological correlates of cognitive and attentional flexibility has substantiated a role for the BG (Leber et al. 2008; van Schouwenburg et al. 2010b, 2012), leading van Schouwenburg et al. (2012, 2014) to propose that frontal cortex, particularly DLPFC, controls striatal function through dense topographically organized projections, and that these projections are crucial to cognitive flexibility.

Indeed, even in the absence of PFC, the BG can maintain flexibility. Lesion experiments in primates have demonstrated that flexible and contextually appropriate, “intellectual” behavior and curiosity are retained even in prefrontally decorticated animals, albeit with a surfeit of reactivity, provided the BG are preserved (Mettler 1945). This same series of experiments demonstrated that removal of striatal tissue produces fatuous hyperactivity and incuriosity, noting that “Animals lacking the striatum always display a certain fatuous, expressionless facies from which the eyes stare vacantly and with morbid intentness.” Subsequent bilateral pallidotomy in these animals produced hypokinesia eventually “indistinguishable from periods of sleep”

13. Basal Ganglia Involvement in Cognitive Dysfunction and Collapse

In this section:

13.1. Deficits associated with basal ganglia damage are as diverse and profound as those associated with cortical damage.

13.2. Lesions and inactivations of the BG and associated structures are associated with severe impairments of consciousness and cognitive integrity, and therapies that target the BG can restore coherent consciousness.

13.3. Schizophrenia involves significant disruption of frontostriatal connectivity and associated functionalities.

13.4. Disruption of working memory in schizophrenia resembles that associated with frontocortical lesions and Parkinson’s disease.

13.5. Schizophrenia is characterized by multifarious abnormality of cortical physiology, particularly affecting connectivity hub areas, that may be the result of genetic factors implicating GABA signaling.

13.6. Schizophrenia may fundamentally be a dysfunction of basal ganglia mediated synchronization.

13.7. A classic diagnostic test for schizophrenia may demonstrate behavioral correlates of dysfunctional BGMS.

13.8. Schizophrenia may be a condition of continual surprise.

13.1. Deficits associated with basal ganglia damage are as diverse and profound as those associated with cortical damage.

Evidence from the pathological brain supports the proposition that the BG are functionally coextensive with frontal cortex, critically implicating them in action, awareness, and cognition. Earlier, I noted involvement of BG components in degenerative conditions such as Parkinson’s and Alzheimer’s diseases, and throughout this paper I have noted implication of the BG system in schizophrenia. Also noted earlier, the BG have been implicated in GTS and OCD. Below, I briefly explore additional evidence from clinical and lesion studies, and more thoroughly explore BG involvement in Sz.

13.2. Lesions and inactivations of the BG and associated structures are associated with severe impairments of consciousness and cognitive integrity, and therapies that target the BG can restore coherent consciousness.

Lesions of the BG in humans, particularly of the caudate portion of the striatum, lead to cognitive and behavioral deficits commonly associated with frontocortical lesions—frequently, abulia (loss of mental and motor initiative), disinhibition, memory dysfunction, and speech disturbances including, rarely, aphasia (Bhatia and Marsden 1994). Similar deficits occur with BG-recipient thalamic infarcts involving the MD and VA nuclei (Stuss et al. 1988) and intralaminar nuclei (Van der Werf et al. 1999). Accidental bilateral destruction of the GPi, incidental to treatment for Parkinson’s disease, has resulted in akinetic mutism (Hassler 1982).

Severe disability following brain injuries is consistently associated with selective cell loss in central thalamic nuclei, and as noted earlier, permanent vegetative state (PVS) is associated with loss spanning the rostrocaudal extent of the intralaminar nuclei and MD nucleus (Schiff 1982). PVS is invariably accompanied by diffuse subcortical white matter damage, and is usually accompanied by widespread or severe thalamic damage, but often presents with no apparent structural abnormalities in the cerebral cortex or brainstem (Adams et al. 2000).

PVS is also associated with significant impairment of backward connectivity from frontal to temporal cortex, relative to minimally conscious patients and normal controls (Boly et al. 2011), directly implicating the most
densely BG-recipient areas and layers of cortex. Similarly, anesthesia-induced unconsciousness is associated with disruption of backward connectivity from frontal to parietal cortex (Ku et al. 2011) and, as noted earlier, with inactivation of the intralaminar nuclei (Alkire et al. 2008).

In some patients exhibiting akinetic mutism and other severe deficits associated with the minimally conscious state, administration of the GABA\textsubscript{A} agonist zolpidem has been found to reliably induce substantial but transient recovery, apparently by restoring normal function and oscillatory structure in frontal cortex, striatum, and thalamus (Brefel-Courbon et al. 2007; Schiff 2010). Similar transient recoveries in other patients exhibiting similar symptoms with BG involvement have been reported in response to administration of the DA agonist levodopa (McAuley et al. 1999; Berger and Vilensky 2014).

Perhaps the most remarkable discovery to emerge from various studies of the physiology of reduced or lost consciousness, is that the intralaminar thalamic nuclei, comprising a very small area indeed, are quite indispensable for consciousness (Bogen 1995; Baars 1995; Van der Werf et al. 2002). These are also the thalamic nuclei most intimate with the BG, bearing implications amply explored here.

13.3. Schizophrenia involves significant disruption of frontostriatal connectivity and associated functionalities.

Many diseases are associated with corticostriatal abnormalities (Shepherd 2013), and Sz in particular has been proposed to be fundamentally a dysfunction of cortico-striatal loops, particularly implicating DLPFC and its striatal targets (Robbins 1990; Simpson et al. 2010). It is associated with significant anatomical attenuation of the DLPFC-VS projection, observed in both patients and their asymptomatic siblings (de Leeuw et al. 2015), simultaneous with abnormally elevated functional connectivity in the ventral frontostriatal system, and abnormally attenuated functional connectivity in dorsal frontostriatal systems, both of which are correlated with severity of symptoms, and are likewise apparent in both patients and their asymptomatic first-degree relatives (Fornito et al. 2013). More generally, Sz patients exhibit a characteristic pattern of significant differences in dynamical functional connectivity responses to sensory stimuli, with greater than normal connectivity established for some long range pairs, and less than normal for others (Sakoğlu et al. 2010). Similarly, Sz is associated with deficient BG-mediated disengagement of the default mode network during directed task performance, simultaneous with striatal hyperactivity (Wang et al. 2015).

13.4. Disruption of working memory in schizophrenia resembles that associated with frontocortical lesions and Parkinson’s disease.

Comparisons of spatial WM task performance by patients with frontocortical lesions, PD, and Sz, reveal related and often severe deficits (Pantelis et al. 1997). Sz patients show particularly severe deficits in set-shifting (Jaboe et al. 2007), and significantly attenuated WM capacity (Silver et al. 2003). If, as discussed earlier, WM items are delimited by finely graded phase distinctions (Siegel et al. 2009), then the narrowness and accuracy of temporal discrimination imposes a limit on addressable item capacity. In Sz this selectivity is reduced by dysfunction of GABA-dependent cortical coincidence window mechanisms (Lewis et al. 2005; Gonzalez-Burgos et al. 2015), affecting the dynamics of corticocortical, BGMS, and non-BG-recipient transthalamic paths in similar measure.

13.5. Schizophrenia is characterized by multifarious abnormality of cortical physiology, particularly affecting connectivity hub areas, that may be the result of genetic factors implicating GABA signaling.

While L3 pyramidal neuron dendritic spine density in the normal brain is particularly high in PFC (Elston 2000), Sz is associated with significant decrease of spine density in DLPFC deep L3 (Glantz and Lewis 2000), and with atrophy of PFC pyramidal somata in L3 and L5, from which corticocortical projections arise (Rajkowska et al. 1998). More generally, Sz is associated with pervasive and progressive compromise of cerebral white matter integrity (Lim et al. 1999; Mori et al. 2007), particularly impacting long range links associated with connectivity hub areas of cortex (Collin et al. 2014). While abnormal hub area anatomical connectivity is most pronounced in individuals affected directly by the disease, the unaffected siblings of Sz patients also show significant attenuation of these links, relative to normal controls, even while connectivity in non-hub areas is unaffected in siblings, and is not significantly affected in Sz (Collin et al. 2014; de Leeuw et al. 2015). These patterns imply a large genetic component to the disease, and an etiology that implicates mechanisms of connectivity that are specific to hub areas, which as noted earlier include areas that are particularly dense targets of BG output.

Cerebral disintegration in Sz may be rooted in GABAergic dysfunction, and consequent pervasive oscillatory deficits (Lewis et al. 2005; Ferrarelli and Tononi 2011; Gonzalez-Burgos et al. 2015; Uhilaas and Singer 2010). GABA dysfunction disrupts the synchronies to which the cortex and striatum respond, the mechanisms whereby the BG modulate spike timing in their targets, and the time alignments between corticocortical and trans-
BG spike volleys that are necessary for BGMS. Moreover, corticostrial projections to striosomal SPNs, as to matrical SPNs, synapse sparsely, with high thresholds for discharge, resulting in similar sensitivity to input synchronies (Kincaid et al. 1998; Zheng and Wilson 2002). As noted earlier, striosomes and PFC are arranged in recurrent dopaminergic loops. Thus synchronal abnormalities in inputs to striatum likely produce dopaminergic dysregulation, and associated dynamical dysfunction and pathological expressions of plasticity, constituting a key mechanism for pathological progression. While therapies targeting GABA have thus far produced modest and mixed results, continued development may lead to effective prophylactic and genuinely curative drug treatments, with the potential to alleviate the negative and cognitive symptoms that have heretofore robustly resisted treatment (Carpenter et al. 1999; Gonzalez-Burgos et al. 2015; Keefe et al. 2007).

### 13.6. Schizophrenia may fundamentally be a dysfunction of basal ganglia mediated synchronization.

The etiology of Sz, and even the epoch of its emergence as a disease in *homo sapiens*, are notoriously obscure and controversial (Tandon et al. 2008). Sz patients exhibit a variety of seemingly contradictory symptoms, classified generally as positive, negative, and cognitive, with each subject exhibiting an idiosyncratic symptomology (Kay et al. 1987; Simpson et al. 2010). The explanation for this variety and obscurity is readily apparent, if the irreducible etiology of Sz is dysfunction of the highly distributed and heterogeneous BGMS mechanism described here, because a particular initiating syndrome within a particular component of the mechanism would likely result in Sz with a distinct symptomatology.

Whatever the root causes, most components of the BGMS system have been implicated in schizophrenia. Prominent among them are syndromes of the PFC, striatum, frontostriatal connectivity, and DA signaling, as noted above, and of the intralaminar nuclei and their connections to PFC, cortical FSI function, the TRN, the PPN and LDT, the cholinergic system generally, and the 5-HT system, noted earlier. Also implicated are left-lateralized GP hyperactivity (Early et al. 1987), cytological and neurochemical anomalies in the BG-recipient and associative thalamus more broadly (Cronenwett and Csernansky 2010), aberrant functional connectivity of thalamus with cortex generally (Cheng et al. 2015), and abnormalities in the gross anatomy of the basal ganglia (Mamah et al. 2007). If any of these components is disrupted, the capacity for BGMS to appropriately establish and dissolve effective connections in cortex, and regulate the dynamics of existing connections, is disrupted in some fashion.

### 13.7. A classic diagnostic test for schizophrenia may demonstrate behavioral correlates of dysfunctional BGMS.

Proverb comprehension was the basis of some early diagnostic tests for Sz, and while in clinical practice these tests have proved unreliable, a more recent study demonstrated a strong correlation between performance on a proverb comprehension task and performance on a theory of mind task, and much better performance on the proverb comprehension task among normal controls than among Sz patients (Brüne and Bodenstein 2005). Proverbs are metaphors, and the successful comprehension of a metaphor entails the recognition of certain abstract semantic relations, simultaneous with the suppression of other, concrete, semantic relations. If these semantic relations are realized physiologically as long range effective connections, then impairment of the supervisory control of effective connectivity would manifest as impaired comprehension of metaphors.

### 13.8. Schizophrenia may be a condition of continual surprise.

The impression that emerges from the various behavioral and physiological anomalies characteristic of Sz, is of a brain that is continually and indiscriminately surprised. Percepts that are normally anticipated or familiar, and ideas that are normally dismissed as absurd, are not appropriately neglected, but instead are given spurious salience, with associated hyperdopaminergia (Kapur 2003; Bromberg-Martin et al. 2010). Subjective duration, causality, sequentiality, and simultaneity, are abnormal and distorted (Martin et al. 2013; Schmidt et al. 2011; Ciullo et al. 2016). These phenomena can all follow from deficiencies in the mechanisms of representation, and these deficiencies plausibly follow from dysfunction in spike-timing-dependent gain mechanisms, which pivot on GABA. Representational deficiency leads to senseless surprise and ideation, and associated maladaptive attentional focus and expressions of plasticity. With expectations and impressions that are fundamentally untrustworthy (cognitive symptoms), paranoia and bizarre behavior (positive symptoms) and indiscriminate withdrawal (negative symptoms) naturally follow. By this narrative, treatment that restores the trustworthiness of expectations and impressions, producing remission of cognitive symptoms, will naturally lead to remission of positive and negative symptoms.
14. Comparisons to Parallel and Related Systems

In this section:
14.1. The Hippocampal System
14.2. The Zona Incerta
14.3. The Claustrum
14.4. The Cerebellum

14.1. The Hippocampal System

In this subsection:
14.1.1. The hippocampal system underlies the formation of episodic memories.
14.1.2. Anatomical terminology in the hippocampal system
14.1.3. Hippocampal lesions compromise the formation of episodic memories, while sparing other mental faculties.
14.1.4. The hippocampal system is organized around oscillations.
14.1.5. The hippocampal system is largely arranged parallel to the BGMS system, with notable similarities and distinctions.
14.1.6. The hippocampal system has a critical role in the assignation of saliency.
14.1.7. The basal ganglia might control effective connection of cortical areas that are chiefly connected through the hippocampal system.

14.1.1. The hippocampal system underlies the formation of episodic memories.

The hippocampal system is thought to function as a persistent associative memory repository of first resort, capturing patterns of cortical network activation representing significant associations as they occur, in close coordination with prefrontal cortex (Battaglia et al. 2011; Rolls 2010; Squire 2004; Damasio 1989; Meyer and Damasio 2009). Subsequent to initial encoded storage in the hippocampal formation, these associations are for a limited time available for retrieval (reactivation of the original cortical pattern), both to contribute to mental activity during wakefulness when relevant, and for migration to less labile (and more capacious) areas outside the hippocampus (Frankland and Bontempi 2005). This process of migration is believed to occur mostly or entirely during sleep (Battaglia et al. 2011; Rasch and Born 2013).

The special facilities of the hippocampal formation follow in part from its unique plasticity (Martin and Morris 2002; Deng et al. 2010; Snyder et al. 2005; Shors et al. 2001; Cameron and Mckay 2001; Hastings and Gould 1999) and its exceptional capacity for long-range functional connectedness (Lavenex and Amaral 2000; Mišić et al. 2014).

14.1.2. Anatomical terminology in the hippocampal system

In this brief treatment, the term “hippocampal formation” refers to the collection of medial temporal lobe areas that are functionally and spatially contiguous with the hippocampus proper, namely the dentate gyrus, hippocampus, subiculum, presubiculum, parasubiculum, and entorhinal, perirhinal, and parahippocampal cortices (Lavenex and Amaral 2000). The “hippocampal system” comprises the hippocampal formation, the thalamic midline and anterior nuclear groups, the mammillary bodies, the septal nuclei and diagonal band of Broca, and the circuitry interconnecting these loci, particularly the fornix. It also implicitly includes the connections of these areas to the rest of the brain.

14.1.3. Hippocampal lesions compromise the formation of episodic memories, while sparing other mental faculties.

Bilateral lesions destroying or disabling the hippocampal formation are associated with severe anterograde amnesia and graded retrograde amnesia, but spare intellectual, attentional, and most working memory capacities, motor skill learning, and semantic and other non-episodic memory, and are not associated with any apparent progressive deterioration, neither of the initially unaffected mental faculties, nor of brain physiology outside that directly affected by the initial lesions (Schmolck et al. 2002; Corkin 2002; Annese et al. 2014). This pattern of deficits shows that the function of the hippocampal formation is highly specialized. Moreover, that function is not contingent on conscious engagement (Henke 2010). Yet memory processing by the hippocampal formation entails sensitivity to and activation of widely distributed networks, close integration with PFC, profuse projections to the ventral BG (Brog et al. 1993), profuse
innervation by midbrain DA centers (Gasbarri et al. 1996), and consolidation processes implicating widely
synchronized thalamocortical signaling, all of which it shares with the highly generalized BGMS system
described here. Moreover, long-term memory deficits in
general, and hippocampal system dysfunction in particular,
have been multifariously implicated in Sz as vulnerability
indicators and primary symptoms (Holthausen et al. 2003;
Harrison 2004; Seidman et al. 2003; Sigurdsson et al.
2010). Thus, though the functional domain of the
hippocampal system is circumscribed, many of its
operating principles and physiological underpinnings are
shared with the BG-thalamocortical system.

14.1.4. The hippocampal system is organized around
oscillations.

Oscillatory activity, and sensitivity to phase, have been
amply demonstrated in the hippocampal system and in
long term memory processing (Fell and Axmacher 2011;
Colgin 2011; Tort et al. 2008; Fernandez et al. 2013).
Information flow in the hippocampal system appears to be
systematically organized around theta oscillation, with
encoding of new incoming information at antiphase with
retrieval of past information (Siegle and Wilson 2014;
Hasselmo et al. 2002; Wilson et al. 2015). Rhythmic
coordination of hippocampus and striatum has been
demonstrated during learning (DeCoteau et al. 2007), and
hippocampus and PFC exhibit increasingly synchronized
oscillation as rules are acquired in a task framework, with
peak coherence at the moment of decision; during
subsequent sleep, hippocampal cell assemblies that
participated in the coherent oscillation during performance
are preferentially replayed (Benchenane et al. 2010).

14.1.5. The hippocampal system is largely arranged
parallel to the BGMS system, with notable similarities and
distinctions.

It seems plausible, even likely, that reactivation of
connectivity patterns by the hippocampal system entails a
BGMS-related mechanism pivoting on relays through the
thalamus, particularly implicating the midline and anterior
nuclear groups. Components of the hippocampal system
project to all of the midline nuclei, which in turn project to
superficial and deep layers of most cortical areas, and to
the ventral striatum (Van der Werf et al. 2002). Notably,
BG direct path and hippocampal system inputs are
mutually exclusive in the midline and intralaminar nuclei,
each nucleus innervated by one or the other, but not both
(Van der Werf et al. 2002). The midline nuclei, like the
intralaminars, are well-positioned to control cortical
synchronies and associated effective connectivity
(Saalmann 2014).

The anterior nuclear group is densely and reciprocally
linked with the hippocampal formation, and like the
midline nuclei, is devoid of BG direct path inputs
(Jankowski et al. 2013). These nuclei are also devoid
of projections to the BG, but project extensively to neocortex,
particularly to secondary motor, prefrontal, cingulate,
retrosplenial, and some visual and temporal areas
(Jankowski et al. 2013), many of which are also targeted
by BG-recipient thalamus.

While inputs to the BG-recipient thalamus arise from
the entire cortex, cortical inputs to the midline and anterior
nuclei are highly restricted, confined almost entirely to the
hippocampal system, despite projections from these nuclei
encompassing nearly the entire cortex (Van der Werf et al.
2002; Jankowski et al. 2013). Thus, whereas BGMS is
proposed to attend the control of arbitrary corticocortical
connectivity, involvement by the hippocampal system in
the initial reactivation of a memory likely entails only
signals from the hippocampal formation to neocortex,
directly and via transthalamic paths through the midline
and anterior nuclei.

The obvious suggestion is that the midline nuclei and
anterior nuclear group function within the hippocampal
system the way the intralaminar nuclei and MD, VA, VL,
and VM nuclei function within the system described by the
BGMS model, with both systems operating chiefly by the
spike-timing-dependent mechanisms endemic to the
cerebral cortex, thalamus, and striatum. The PFC and
ventral striatum, jointly targeted by the hippocampal
formation and by thalamic and other nuclei in both
systems, are then positioned to coordinate activity in these
two vast and largely separate systems, particularly by
incorporating motivation and behavioral relevance into the
control of memory formation and activation. BG influence
on hippocampal system activity is implied by projections
from the BG-recipient PC and PF nuclei to perirhinal,
entorhinal, prelimbic, and parahippocampal cortices (Van
der Werf et al. 2002). Additionally, the paraventricular and
reuniens nuclei of the midline group receive dense
projections from midbrain DA centers (Van der Werf et al.
2002), whereby the BG presumptively align memory
dynamics with motivational context, while the central
medial nucleus of the intralaminar group receives
hippocampal system inputs (uniquely among nuclei
classified as “intralaminar”), and projects densely to the
dorsal striatum (Van der Werf et al. 2002), suggesting
episodic memory contextualization of dorsal BG inputs.

A notable architectural distinction between these two
systems is that hippocampal formation input to thalamus is
excitatory, like neocortical inputs to BG-recipient
thalamus, whereas BG input is GABAergic. Thus the
selection and timing of signals to be dispersed by the
midline and anterior nuclei is presumptively determined
before those signals arrive in thalamus, consistent with the
much narrower array of inputs compared to BG-recipient
thalamus. However, TRN inputs to these nuclei
(Jankowski et al. 2013; Kolmac and Mitrofanis 1997; Van
der Werf et al. 2002) likely provide a path whereby PFC
and the BG can influence memory processes at the thalamic level (Pinault 2004; Zikopoulos and Barbas 2006; Guillery et al. 1998; Hazrati and Parent 1991; Shammah-Lagnado et al. 1996; Antal et al. 2014).

14.1.6. The hippocampal system has a critical role in the assignation of saliency.

Indeed, just as the PFC and BG may orchestrate BG-thalamocortical neglect of expected percepts (discussed earlier), PFC has been suggested to orchestrate neglect by the hippocampal formation of previously stored episodic information, inhibiting redundant memorization (Frankland and Bontempi 2005). Moreover, the hippocampal formation is itself sensitive to familiarity (Squire 2004), and through its projections to PFC and the ventral striatum, may promote neglect of familiar perceptual minutiae that would otherwise be distracting. Sz is marked by deficiencies in these capabilities, and corresponding hippocampal abnormalities (Jessen et al. 2003; Weiss et al. 2004).

14.1.7. The basal ganglia might control effective connection of cortical areas that are chiefly connected through the hippocampal system.

The most studied and attested roles of the hippocampal system involve memory formation and recall, but the mechanism whereby it is understood to do this — rapid plasticity that establishes long range links between cortical areas — might be quite general. In terms of BGMS, it may not make any fundamental difference whether two areas are linked by direct, appropriately potentiated corticocortical projections, or by temporary routes through the hippocampal system. Indeed these two classes of long range linkage inevitably coexist according to the consolidation and reconsolidation theories of hippocampal function, and might indeed act synergistically. With hippocampal function centered on the rapid establishment of long range anatomical connections amenable to reactivation, BG function entailing the activation of long range anatomical connections, and PFC integral to the circuitry of both, it seems inevitable that these two systems are unified in their function. This proposition does, however, raise important questions about conduction delays associated with trans-hippocampal paths, compared to those of the corresponding corticocortical paths that are thought to be the ultimate destination of the relations migrated by consolidation.

14.2. The Zona Incerta

The zona incerta (ZI) is an agglomeration of cytologically heterogeneous diencephalic nuclei below the thalamus, adjacent to the TRN and STN, connected with many of the areas and populations involved in BGMS (Mitrofanis 2005; Ricardo 1981; Shammah-Lagnado et al. 1985). Multiple, overlapping somatotopic maps are found throughout the ZI, maintaining largely parallel segregated circuits between the neocortex, thalamus, superior colliculus, brainstem, and spinal cord (Nicolelis et al. 1992; Power et al. 1999), but with no apparent topographic structure in projections to intralaminar thalamus (Power et al. 1999). Like the striatum, the ZI is extensively innervated by cortical layer 5 (Mitrofanis and Mikuletic 1999). Like the GPi and SNr, many of its neurons contain parvalbumin (Trageser et al. 2006), and it has extensive GABAergic projections to thalamus, with giant terminals apposing the proximal dendrites of projection neurons in association nuclei (Barthó et al. 2002; Power et al. 1999).

The physiology of the ZI is unlike that of the BG and TRN in several important respects, such that its operating principles are clearly distinct. Unlike either the BG or the TRN, the ZI has direct projections to cerebral cortex; these projections are GABAergic, predominantly appose outer L1, are topographically organized, are densest in somatosensory cortex, and also project sparsely to visual cortex (Lin et al. 1997). While BG projections to intralaminar nuclei preferentially appose smaller and more distal dendrites, ZI projections to the intralaminar thalamus appose larger and more proximal dendrites (Barthó et al. 2002). The tonic discharge rate of ZI neurons, averaging 2-4/s (Périer et al. 2000; Trageser et al. 2006), is a small fraction of that of GPi/SNr projection neurons.

Like the BG and thalamus, the ZI is targeted by cholinergic projections from the PPN and LD (Trageser et al. 2006), and like the cortex, it is targeted by the basal forebrain (Kolmac and Mitrofanis 1999), but the effect of ACh on ZI is to silence it (Trageser et al. 2006). Thus the ZI response to ACh resembles that of the TRN (Steriade 2004; Lam and Sherman 2010). However, whereas the TRN receives collaterals of L6 axons and not of L5 axons, and has a reciprocal relationship with the rest of the thalamus, as noted above the ZI receives L5 collaterals, and it does not receive thalamic inputs (Barthó et al. 2002).

Through its widespread projections to thalamus, the ZI has been suggested to synchronize oscillations in large populations of projection cells, acting as a relay whereby signals from its afferents can selectively facilitate transmission of sensory signals by those projection cells (Barthó et al. 2002, 2007). Experimental and clinical results in PD show that hyperactivity and hypersynchrony in the ZI are associated with dyskinesia and bradyphrenia just as in the GPi and SNr (Merello et al. 2006; Périer et al. 2000, 2002), and indeed that deep brain stimulation (DBS) in ZI may be a more effective technique for alleviating medically refractory PD than DBS in STN (Plaha et al. 2006).
An intriguing proposal is that rhythmic GABAergic input to the sensorimotor and intralaminar thalamus from ZI relays activity from attentional orientation centers such as the superior colliculus, disrupting BG-related activity in the thalamus and replacing it with selective receptivity to unexpected sensory inputs deemed salient by attentional orientation centers (Watson et al. 2015). This fits well with the proposition that the general function of the ZI is to gate sensory receptivity (Tragesser and Keller 2004; Tragesser et al. 2006; Lavallée et al. 2005; Urbain and Deschênes 2007), and like BGMS, is a proposal that selections can be made in the thalamus by GABA-mediated spike-timing-dependent gain control. And with its GABAergic projections to upper L1, the ZI is positioned to adjust spike-timing-dependent gain in its targets with particular rapidity and thoroughness.

14.3. The Claustrum

The claustrum may be functionally similar to the ZI and, by extension, to the BG, but with its own peculiarities. It has long been a subject of notoriously inconclusive study (Edelstein and Denaro 2004). Its function is murky, and like the ZI, it is something of a chimera, combining physiological and functional attributes of the cerebral cortex, the striatum, the thalamus, and the basolateral amygdala (Swanson and Petrovich 1998). Like the BG, the claustrum appears arranged to synchronize the cortical areas with which it is connected, but unlike the BG, it appears to do so only occasionally. In particular, unlike pallidal projection neurons, and like ZI projection neurons, claustral projection neurons have a low tonic firing rate, 0-10 spikes/s in awake animals (Edelstein and Denaro 2004 p.5).

The claustrum contributes to the recruitment of a generally well-adapted neural response to novel and unexpected situations (Badiani et al. 1998; Remedios et al. 2014), and to emotionally freighted stimuli (Redouté et al. 2000), by orienting attention toward immediate, external sensory specifics. Similar to the ZI, it reciprocates with topographic cortical maps for all of the exteroceptive senses; the implicated claustral neurons have quite large receptive fields, with some incidence of polymodality (Sherk 1986). The entire claustrum is modulated by afferents communicating situational saliency (exceptionality) from VTA and SNC, the thalamic reuniens nuclei, the lateral hypothalamus, the locus coeruleus, the dorsal raphe nucleus (Sloniewski et al. 1986), and through some path yet to be fully anatomically elucidated, from a cholinergic source (Salerno et al. 1981; Nieoullon and Dusticier 1980) that is almost certainly in the basal forebrain cholinergic complex, whence arise widespread projections to the olfactory bulb, hypothalamus, amygdala, all parts of cortex (Mesulam et al. 1983), and much of the thalamus (Kolmac and Mitrofanis 1999).

Perhaps claustral neurons synchronize oscillations between and within activity in the cortical areas that reciprocate with them, similar to the dynamic described earlier in the thalamocortical projection. In the claustrum, however, the effect appears to be well-gated by the ascending modulatory afferents, resulting in the low tonic firing rate noted above. This is a limited role, similar to a general role proposed previously for the claustrum (Crick and Koch 2005), itself similar to the role ascribed to the BG in this paper.

The cortical areas with which the claustrum has been established to reciprocate, and which are therefore most likely to be be subject to synchronization in the manner of thalamocortical circuits, are (1) various topographically mapped unimodal sensory areas for each of the senses (at least the exteroceptive ones) (Sherk 1986), (2) the frontal eye fields and supplementary motor area (SMA) (Sherk 1986), (3) several default mode network loci (orbitofrontal, cingulate) (Sherk 1986), and (4) the hippocampal system (Wilhite et al. 1986). There are also convergent afferents from thalamic midline and intralaminar nuclei (reuniens, CM, PF, PC, CL) (Van der Werf et al. 2002). When the cholinergic, noradrenergic, dopaminergic, serotonergic, and other diffuse modulatory claustralpetal afferents signal situational or anticipated salience (Salerno et al. 1981; Schultz 1998; Matsumoto and Hikosaka 2009; Nakamura et al. 2008), claustral neurons might attempt to synchronize activity in the sensory stream with itself, with oculomotor and skeletomotor activity, with the default mode network, and with the hippocampal system, so that the situation and its sensory correlates are well-attended, consciously integrated, and well-reflect by the memories that are activated and recorded.

In a recent study (Grasby and Talk 2013), the intimate involvement of the claustrum in spatial reversal learning was clearly demonstrated. This comports with the excitatory effect of dopamine depression on the claustrum (Salerno et al. 1981), and the systematic coupling of dopamine reduction with failures to predict outcomes (effectively, surprises and disappointments) (Schultz 1998). The claustrum also has unreciprocated projections to much of the rest of cortex, notably area 46 (DLPFC) (Sherk 1986), which might impart selective receptivity in the recipient areas to sensory and motivational activity that activates the claustrum, selectively boost cognitive activity that is already phase-locked with it, and relatively diminish other activity.

14.4. The Cerebellum

There is evidence that the cerebellum, like the BG, targets both superficial and deep cortical layers, via separate nuclei; in particular, the fastigial nucleus targets superficial layers as part of a putative diffuse activating system (Steriade 1995). The cerebellum is reciprocally linked with
the BG and cerebral cortex (Bostan and Strick 2010; Bostan et al. 2013), and forms closed loops with cortex via the thalamus, like the BG (Strick et al. 2009; Glickstein et al. 1985; Schmahmann and Pandya 1997). The cerebellum seems to be functionally coterminal with the BG, including extensive and varied cognitive and other non-motor roles (Strick et al. 2009; Schmahmann and Pandya 1997). The cerebellum learns associatively, and in particular, learns predictive relations underlying forward control in stimulus-response behaviors (Giovannucci et al. 2017). And indeed, the cerebellum has been implicated in Sz (Andreasen et al. 1998; Andreasen and Pierson 2008).

However, the cerebellum is not necessary for coherent thought and behavior, as this is preserved with manageable and finite deficits even in cases of complete cerebellar agenesis (Yu et al. 2015). In primates, the white to gray matter ratio is lower in cerebellum than in neocortex (in chimpanzee, 0.24 and 0.64 respectively), and across mammalian taxa the scaling exponent of that ratio is significantly lower in cerebellum than in neocortex (1.13 and 1.28 respectively) (Bush and Allman 2003). The cerebellar cortex does not form links with itself (Bush and Allman 2003), suggesting that the cerebellum has little or none of the flexible associativity and analogical processing power characteristic of the neocortex in particular and the forebrain in general.

Nonetheless, the pervasive involvement of the cerebellum in precision motor learning and sensory-motor coordination was established generations ago (Ito 2002). The extreme regularity of its physiology has long inspired mechanistic, computational models of its function (Cheron et al. 2016), and oscillatory synchronies between the cerebellum and the cerebrum are recognized and proposed to be functionally significant (Courtemanche et al. 2013; Cheron et al. 2016). The cerebellum and BG have similar topological relationships to cortex, suggesting that they may affect cortical activity by similar mechanisms. In particular, cerebellum-mediated synchronization might induce effective connections.

15. Future Directions, Open Questions, and Closing Thoughts

In this section:

15.1. Theoretical Predictions and Proposed Experiments
15.2. Some Notable Open Questions
15.3. Conscious Cognition and BGMS
15.4. Closing Thoughts
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15.1. Theoretical Predictions and Proposed Experiments

In this subsection:

15.1.1. Cortex and Striatum
15.1.2. Pallidal and Nigral Output to Thalamus
15.1.3. Stimulus-Locked Spiking From Cortex Through Basal Ganglia to Thalamus
15.1.4. Correlation of Cortical Area to Focally Targeted Striatal Area as a Function of Oscillatory Band

15.1.1. Cortex and Striatum

In the BGMS model, effective connections are established in cortex in response to striatal decisions. This phenomenon would likely be detectable in the relationships among cortical and striatal LFPs, and would inherently be detectable using large electrode arrays to measure single unit activity in large populations of neurons in cortex and striatum. Specifically, in well-trained tasks, a highly significant relationship of consistent delays should be found between the timing of a spike volley arising in a particular cortical locus, the presence and timing of subsequent spike volleys arising in one or more connected striatal loci, and the establishment of an effective connection from the first cortical locus to others as measured by LFP or individual spike activity in the latter. In some experimentally accessible and reliably reproducible scenarios, the establishment of a long range corticocortical functional connection is predicted to be strongly contingent on the occurrence and precise timing of the striatal activation, as suggested by the results reported by van Schouwenburg et al. (2010b). The BGMS model predicts that if the striatal activation is absent or mistimed, the connection is unlikely to be established, else the connection is likely to be established. While experiments of this type cannot fully validate the BGMS model, done carefully they can decisively invalidate it, or provide highly suggestive evidence for it. Moreover, raw LFP and spike data sets for experiments that have already been performed can likely be reanalyzed to look for this phenomenon.
15.1.2. Pallidal and Nigral Output to Thalamus

The central prediction arising from the BGMS model is that relationships of entrainment characterize sparse ensembles of directly connected neurons spanning the entire BG direct path during activation. If the effect of pallidal and nigral output on the thalamus is probed in awake healthy (normal) animals, the prediction is that phasic activation in many cases entrains thalamic activity. Preliminary results reported by Schwab (2016) give evidence of ensemble phasic entrainment of motor thalamus by the GPi, while underscoring that spatiotemporal sparseness and stochasticity in this activation and entrainment greatly complicate characterization at the single unit level.

15.1.3. Stimulus-Locked Spiking From Cortex Through Basal Ganglia to Thalamus

Another key prediction is that in an over-trained task, phasic pallidal spiking to a particular thalamic target associated with onset of a particular salient context within the task will exhibit, in aggregate, a very stable, narrowly distributed (±<2 ms) delay relative to the first cortical spike volley associated with onset, implicating a stable set of striatal and pallidal/nigral neurons, for environmental conditions and level of arousal similar to those that prevailed during training.

15.1.4. Correlation of Cortical Area to Focally Targeted Striatal Area as a Function of Oscillatory Band

Because the average delay through trans-GPi paths is roughly one gamma period, while the average trans-SNr delay is roughly one beta period, BGMS predicts functional prominence of the gamma cycle in a cortical area and scenario when its inputs to BG flow primarily to the GPi (particularly implicating the dorsal sensorimotor striatum), while the beta cycle is expected to dominate when activity flows primarily to the SNr (implicating the associative striatum). Even longer delays, commensurate with the theta cycle, may accompany paths through the ventral striatum and pallidum, due to its intimacy with the medial temporal lobe (briefly reviewed below). More generally, according to BGMS the dominant oscillatory band of activity in a given cortical locus and context should be the best predictor of the BG paths it activates, and the converse should hold similarly.

Cross-frequency coupling has been demonstrated in theta band interactions of the hippocampus with striatum (Tort et al. 2008), and is posited to be a general theme in BG-thalamocortical dynamics (Cannon et al. 2014; Brittain and Brown 2014). Putative cross-frequency BGMS operates by spike time dependent gain in cortex no less than in-band BGMS, suggesting the corollary prediction that cross-frequency coupled BG activity in over-trained tasks produces spike volleys in target areas that are spatiotemporally coincident, at a regular frequency ratio, with selected corticocortical spike volleys. Heavy projections from the hippocampal formation to the ventral striatum (Brog et al. 1993) suggest that the in-band relationship may hold in these scenarios, i.e. that the dominant band of the afferent determines the activated BG path at the striatal stage, with divergence to a parallel path in a subsequent stage.

15.2. Some Notable Open Questions

Lag-free long range synchronies in cortex (e.g. Vicente et al. 2008), with narrow pyramidal somatic coincidence windows (Pouille and Scanziani 2001; Volgushev et al. 1998), exist simultaneous with finite long range corticocortical delays (e.g. Gregoriou et al. 2009; Nowak and Bullier 1997). Exactly how does this work, at the level of cortical microcircuitry? How do the discharge and conduction delays of thalamocortical neurons and fibers compare as a function of nuclear origin? In particular, how do the delays of paths through the intralaminar and midline nuclei compare to those through other thalamic nuclei?

Gamma synchrony accompanies effective corticospinal activation (Schoffelen et al. 2005; Fries 2005). The pedunculopontine nucleus is integral to the control of voluntary movements (Tsang et al. 2010), and is profusely targeted by the GPi (Parent et al. 2001). Does this relationship entail BGMS? The same question applies to BG targeting of the superior colliculus, with regard to its attentional orientation and oculomotor functions.

Do the amygdala, hypothalamus, and other subcortical structures beyond those reviewed above, use a BGMS-like mechanism to influence thalamocortical activity? The amygdala in particular has been construed as parallel to the ventral BG (Olmos and Heimer 1999), and indeed its central and medial nuclei are proposed to be continuous and homologous with the BG (Swanson and Petrovich 1998). Moreover, projections from the amygdala to PFC have been shown to convey signals that bias decision making (Burgos-Robles et al. 2017), similar to the role ascribed earlier to the BG.

The BGMS model implies an elaborate physiological arrangement of coordinated modularity, spanning all developmental levels, and many distinct neurotransmitter systems. How is this orchestrated? Rules governing the self-organization of projecting fiber populations and appositions must play a large part (e.g. Wedeen et al. 2012; Sanes and Yamagata 2009; de Wit and Ghosh 2015). But clearly, developmental exuberance, and activity-driven, correlation-sensitive plasticity must play a very large role. Exactly how are these development and plasticity mechanisms arranged to route and terminate...
long range fiber bundles appropriately, and optimize the timing of the stimulus-response functions of the BG as an ensemble?

How strong and broad is the BG influence on the cholinergic and serotoninergic supplies to thalamus, cortex, and striatum? Are the BG arranged for bipolar control of these supplies, as they are for dopamine? What are the topographies and microcircuitry of the BG inputs to TRN, NBM, PPN, LDT, DRN, MRN, and SC, by reference to the topographies and microcircuitry of their respective projections to and from thalamus and cortex?

The cytology and microcircuitry of the striatum are crucial to BGMS, and to basal ganglia dynamics in general. How do the cortico-FSI and cortico-SPN projections to striatum differ in cytological, laminar, and areal origin, in patterns of preference, apposition, and topography/convergence/divergence, and by compartmental and hodological target (matrisome, striosome, border region, direct, indirect, etc.)? Similarly, how do thalamo-FSI and thalamo-SPN projections differ by these measures?

What are the functions of striatral neuron types beyond the SPNs, FSIs, and ACh interneurons, particularly as they relate to BGMS? In particular, what are the roles of somatostatin-positive LTS interneurons, and of calretinin-positive interneurons, which have yet to be classified physiologically (Kreitzer 2009)? Uniquely human adult neurogenesis of striatal calretinin interneurons (Ernst et al. 2016) is intriguing — does this have a particular relation to similar, uniquely human, postnatal interneuron migration to frontal cortex (Paredes et al. 2016)?

Is oscillatory phase preserved in the paths through STN, GPe, NBM, SNI, and PPN/LDT, and if so, do they entrain their targets? Do the BG, through some paths, entrain targets to antiphase, to quickly and decisively abolish connections? Is this one of the functions of FSIs that target indirect path SPNs? Indeed, is this one of the functions of GPe input to striatum (which preferentially innervates FSIs) and TRN, and of STN to GPi/SNr? Such arrangements seem plausible, but the evidence is as yet tenuous—albeit tantalizing (e.g. Schmidt et al. 2013).

The maximum conduction velocity in human corpus callosum is anomalously slow (Caminiti et al. 2009). Are interhemispheric dynamics in humans special, from a BGMS perspective, or otherwise?

15.3. Conscious Cognition and BGMS

In this subsection:

15.3.1. Consciousness is tricky.
15.3.2. Associative areas of the thalamocortical system and BG plausibly underlie consciousness.
15.3.3. Highly abstract functional structure within the most associative areas of neocortex suggests the outlines of mental architecture.
15.3.4. Densely interconnected, highly associative frontal and posterior areas, with no intrinsic domain-specific functional topography, act as communication thoroughfares integrating activity with great flexibility.
15.3.5. BG integration with cortical communication thoroughfares may underlie the versatility that is the hallmark of consciousness.
15.3.6. Large scale plasticity in cortex implicates consciousness and BGMS.
15.3.7. Mammalian consciousness is presumptively one family of instances among many, each family distinct but sharing a set of irreducible architectural features.
15.3.8. The architecture of natural consciousness can inform the design of artificial problem-solving systems.

15.3.1. Consciousness is tricky.

“Consciousness” is a notoriously slippery concept, even chimerical in many accounts. These narrative tribulations seem to be evidence of the fundamental qualities of conscious cognition. Where consciousness is broached above, most prominent are flexibility, integration and the breaching of modularity, intervention when modular strategies are flummoxed, and perhaps most unsettling, arrangements of notionally infinite recurrence. For present purposes, I construe it to be any mechanism that combines the partly overlapping attributes and facilities of unitarity, representation, genericness, ephemeral specificity, arbitrary associativity, intentionality, attention, perception, episodic continuity, and action. Evidently, conscious actions can be inwardly directed (chiefly, cognitive transformations, recollections, memorizations, and decisions, all relative to current patterns of activity) or outwardly directed (behaviors). Reportability and self-awareness, frequently attributed specially to human consciousness, are (by the present narrative) corollary. “Unitarity” signifies particularly that there is only one consciousness in the normal waking brain (largely a corollary of its arbitrary associativity, and the physiology underlying that facility), and that the representations and
core mechanisms of conscious cognition lack any architectural modularity dividing them into perceptive, cognitive, and active domains, but rather that these domains are all directly and irreducibly implicated by the same physiological substrate (as seen, for example, in the thalamic intralaminar nuclei, noted earlier). Patterns of activity ephemerally represent arbitrary patterns of modularity, bounded only by the representational capacity of the system. For a discussion of the capacities at issue, and of the inextricable entanglement within consciousness of the attributes and facilities attributed to it above, see Engle (2002).

15.3.2. Associative areas of the thalamocortical system and BG plausibly underlie consciousness.

The integrated system of the PFC and striatum, suggested to be central to cognitive flexibility (Leber et al. 2008; van Schouwenburg et al. 2010b, 2012, 2014; Hazy et al. 2006), includes many connectivity hubs and resting state network nodes (Cole et al. 2010; van den Heuvel and Sporns 2011; Harriger et al. 2012; van den Heuvel et al. 2009; Elston 2000). Indeed, correlated activity has been demonstrated between cortical resting state network nodes and loci distributed widely in the striatum (Di Martino et al. 2008; Vatansever et al. 2016). Within the network of connectivity hubs, particular areas and networks have been identified that are associated with facilities attributed above to consciousness. For example, Vincent et al. (2008) propose a “frontoparietal control network” comprising lateral PFC, anterior cingulate cortex, and the inferior parietal lobule, topographically and topologically separate from the hippocampal network and “dorsal attention” network. PFC and posterior parietal cortex in particular have been implicated in theories of the physiological basis of fluid intelligence (Jung and Haier 2007).

In general, the establishment of functional connections between dissociable networks, heralding a collapse of their mutual modularity, is associated with conscious awareness (Godwin et al. 2015), while pharmacologically induced loss of consciousness is associated with the pervasive breakdown of effective connectivity in cortex (Ferrarelli et al. 2010b).

15.3.3. Highly abstract functional structure within the most associative areas of neocortex suggests the outlines of mental architecture.

It has been proposed that PFC is organized into a spatially graded hierarchy, with the highest and most abstract representations located anteriorly, and the lowest and least abstract located posteriorly (Christoff and Gabrieli 2000; Badre and D’Esposito 2009). In the least abstract of these areas, numerous visuotopic maps (for example) have been identified (Silver and Kastner 2009). Functional specialization of the dorsomedial and dorsolateral PFC has been proposed, with the former monitoring performance, and the latter guiding it; links between these areas exhibit mutual preferences according to position along the anterior-posterior axis (Taren et al. 2011). Within the DLPFC, subdivisions are apparent from their functional correlates and network connectivity—an anterior-ventral subregion is associated with attention and action inhibition processes, and is intimate with anterior cingulate cortex, while a posterior-dorsal one is associated with action execution and working memory, and is intimate with posterior parietal cortex (Cieslik et al. 2013). Clearly this topographic and topological structure has consequences for mental architecture. Indeed, the microstructural characterization of projections between hub areas is among the most promising subjects for future investigation.

15.3.4. Densely interconnected, highly associative frontal and posterior areas, with no intrinsic domain-specific functional topography, act as communication thoroughfares integrating activity with great flexibility.

Perhaps anterior PFC, and the posterior parietal cortex intimate with it, contain areas in which domain-specific functional topography is a purely transitory consequence of their effective connections from moment to moment, given highly abstract topographies along lines of hierarchy and generic aspects of cognition. Such an arrangement is implied by the suggestion that individual neurons, and indeed individual synapses, can participate in a vast array of distinct ephemeral assemblies of neurons with contextually appropriate conduction delays (Izhikevich 2006). This also comports with the view of van den Heuvel et al. (2012) that a core network of connectivity hubs (a “rich club”) serves as a common, and therefore contentious, communication “backbone” subject to “greedy routing” strategies by more locally connected (and specialized) areas. Indeed, task-related activity in functionally connected PFC and posterior parietal cortex can be very similar, with almost identical tuning and time courses, throughout the performance of a task implicating working memory (Chafee and Goldman-Rakic 1998). The view that cortical areas with high abstraction and long range connectivity function as thoroughfares also follows from findings noted earlier, that frontal-posterior LFP synchrony accompanies attentional orientation, whether by top-down or bottom-up processes (Buschman and Miller 2007).

15.3.5. BG integration with cortical communication thoroughfares may underlie the versatility that is the hallmark of consciousness.

Activity in particularly abstract areas of the PFC might arrange itself to impart nearly arbitrary patterns to the striatum, inducing highly flexible transformations by the
BG of cortical activity and effective connectivity, and resolving backbone contention through selections. By this narrative, the BG make available an enormous accumulation of neural gestures, effectively tools, that activity in hub areas can use to operate on network activity, particularly activity within itself. The corticostriatal projections from hub areas, and the input-output relations of the targeted areas of striatum, are then the essential substrate for cognitive flexibility, as suggested by van Schouwenburg et al. (2014). Similarly, a correlation has been shown between cognitive flexibility and resting functional connectivity of hub areas to BG (Vatansever et al. 2016). Moreover, significant dysfunction in this relationship, including both deficient cortical control of striatum, and deficient striatal control of cortex, has been shown in Sz (Wang et al. 2015).

As suggested earlier, if working memory items are patterns of activation in PFC, each characterized by a distinct phase angle (Siegel et al. 2009), then—through corticocortical feedback projections and BGMS—the PFC might establish and dissolve effective connections implicating a particular working memory item (effectively, a thought) with little or no interference from, or indeed to, latent items, except when a latent item is selected for integration with an active item. DA under striosomal control, and ACh and 5-HT under PFC and BG control, are also crucial parts of this tool set, dynamically tuning the receptivity, contrast, focus, selectivity, and persistence, of cortical signal paths.

Because inputs to the BG encompass the entire cortex, the BG can respond to activity in areas that are not functionally connected (not synchronized) with activity in conscious areas, and might act to synchronize the former with the latter. In this way, subconscious activity might be boosted into consciousness by BG selections. Indeed this likely describes any reorientation of attention in response to a sensory stimulus, to the degree that the reorientation is BG-mediated, particularly implicating the thalamic intralaminar nuclei.

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15.3.6. Large scale plasticity in cortex implicates consciousness and BGMS.

The propositions that the highest levels of PFC lack persistent domain-specific functional topographies, control the BG with great flexibility, and are directly implicated in conscious cognition, relate to the dynamics of skill learning and performance. Experience-driven skill acquisition entails the reorganization of cortical topography in sensory and motor areas (Buonomano and Merzenich 1998; Kleim et al. 2004). Topographic reorganization seems to necessitate hub areas without fixed functional topography, in order to maintain function while accommodating the shifting semantic correlates of the neurons comprising the implicated map. In principle, long range connections linking shifting maps to generic hubs might enable sensible integration into cognition at every stage of topographic reorganization. The orchestration of topographic plasticity, and functional continuity during that process, likely implicate not only highly abstract areas of neocortex, but also the hippocampal formation, which is extremely labile and exceptionally well-connected (as briefly reviewed earlier), and has direct and transthalamic links to secondary motor cortex (Jankowski et al. 2013; Van der Werf et al. 2002).

Initial performance of a qualitatively new skill depends on the availability and engagement of working memory (Reber and Kotovsky 1997), and is aided by attention to the minutiae of performance (Beilock et al. 2002). Learning the skill does not entail topographic reorganization until late in the process, and initially pivots on activity and plasticity in the BG and cerebellum (Ungerleider et al. 2002), with a crucial role for corticostriatal SPN plasticity (Koralek et al. 2012). Once proficiency is attained, performance can in fact be significantly disrupted by attention (Beilock et al. 2002). If the BG learn precise sensorimotor sequences through practice (Graybiel 1998), and their performance involves finely tuned subcortical loops, then inapt engagement of high-order PFC, supplying disruptive signals to the striatum, seems quite likely to disrupt overall performance. Similar disruption of input patterns to the cerebellum might have similar consequences.

15.3.7. Mammalian consciousness is presumptively one family of instances among many, each family distinct but sharing a set of irreducible architectural features.

It seems likely that the arrangement of high resolution spatially graded feature maps, with a “rich club” topology of dense high resolution interconnections, hub areas some of which are never plastically committed as feature maps, and dynamic timing-based mesoscopic control of effective connectivity and signaling characteristics by a recurrent, highly convergent-divergent multistage subsystem arranged for self-referential reinforcement learning, is not unique to mammals, or even to vertebrates, but rather is the essential architecture of many evolved conscious systems. This prompts the prediction that instances of this architecture are likely wherever there are organisms exhibiting complex and flexible behavior. Birds share major subcortical structures and connections with mammals, including the BG, with similarities and differences some of which were noted earlier (Luo and Perkel 1999; Kojima et al. 2013; Doupe et al. 2005). Capacities for flexible executive control and persistent strategic planning in ravens (Kabadayi and Osvath 2017) suggest these structural commonalities are accompanied by functional ones. Further evolutionarily afield, cephalopods are renowned for their adaptability and contextually appropriate problem-solving behavior (Mather 2008), and for an evolutionary history quite
separate from that of the vertebrates, but in many respects strikingly convergent (Packard 1972).

15.3.8. The architecture of natural consciousness can inform the design of artificial problem-solving systems.

Earlier, I noted parallels between models of naturally evolved conscious cognition (particularly the “global workspace” model of Dehaene and Changeux (2011), the “dynamic core” model of Tononi and Edelman (1998), and the “integrated information” model of Tononi et al. (2016)), and successful machine learning architectures featuring recurrence, genericness, dynamic modularity, and stochasticity (hybrid metaheuristics (Blum et al. 2011) and iterated local search (Lourenço et al. 2003)). Related architectures developed for machine learning, inspired loosely by physiological features of the vertebrate brain, have been particularly successful. For example, artificial neural networks arranged for recurrence, convolutional transformation, adaptive competitive pooling, and hierarchical representation, have proved exceedingly effective in visual scene analysis (Pinheiro and Collobert 2014; Long et al. 2015) and the semantic analysis of verbal dialogues (Kalchbrenner and Blunsom 2013; Kalchbrenner et al. 2014). Clearly, improving our understanding of natural problem solving mechanisms, and translating that understanding to artificial systems, holds enormous promise.
15.4. Closing Thoughts

This paper was originally motivated by a deceptively simple notion, that a mechanistic explanation for cognitive problem solving capacities in mammals can be found in the conjunction of the cerebral cortex and basal ganglia, whose distinct information processing styles produce a synergy far greater than the sum of their parts. At an intermediate level of detail, this notion pivots on several architectural features of the mammalian brain:

- Control of functional connectivity by spike-timing-dependent gain mechanisms, as discussed by von der Malsburg (1981), Singer (1993), Fries (2005), and Larkum (2013);  
- Centrally (thalamically) mediated control of effective connectivity in cortex, as discussed by Jones (2001), Purpura and Schiff (1997), Saalmann (2014), and Salami et al. (2003);  
- Graded semantic maps in cortex with highly regular long range links, as discussed by Huth et al. (2012), Simmons and Barsalou (2003), and Wedeen et al. (2012);  
- A dense connectome with “rich club” organization, as discussed by van den Heuvel and Sporns (2011) and Markov et al. (2014);  
- The primacy of information integration in the mechanisms of cognition, as discussed by Tononi (2004);  
- Convergence-divergence in the basal ganglia, as discussed by Flaherty and Graybiel (1994), Joel and Weiner (1994), Zheng and Wilson (2002), and Mailly et al. (2013);  
- The basal ganglia construed as a central switching mechanism, as discussed by Redgrave et al. (1999);  
- End-to-end spike volley and oscillatory coherency in the BG, as discussed by Berke et al. (2004), Leventhal et al. (2012), and Schmidt et al. (2013);  
- Slow and diverse CVs in paths through the striatum, as discussed by Tremblay and Filion (1989), Turner and DeLong (2000), and Jinnai and colleagues (Yoshida et al. (1993), Kitano et al. (1998)); and  
- Basal ganglia output that entrains activity in its targets, as discussed by Goldberg et al. (2013), Antzoulatos and Miller (2014), and Kojima et al. (2013).

In the course of developing this conjunctive idea, which was of necessity quite vague at the outset, I encountered an array of significant implications, suggesting resolutions to long-standing mysteries and paradoxes in the physiology of the BG, and in the relationship of BG activity to thalamocortical activity.

My conclusion is that activity throughout the cerebral cortex is structured by large scale synchronies that are mesoscopically and globally influenced by the basal ganglia, which themselves respond to large scale cortical synchronies, in an arrangement of continual iteration.

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