Supplementary Material: Functional Anatomy of the Cortico-Basal Ganglia Behaviour Selection System

This supplementary material provides readers with background knowledge to fully comprehend the Cortico-Striatal-Thalamo-Cortical (CSTC) Circuits Hypotheses and Basal Ganglia (BG) Pathways Hypotheses[1]. Here, we describe the 'classical/canonical' understanding of the cortico-basal ganglia behaviour selection system that has informed both sets of hypotheses. We also provide an updated neuroscientific perspective, outlining more complex and integrative functioning of this system. With this new perspective, we aim to inspire novel research questions and hypotheses that better align with the current state of knowledge and address the limitations of previous hypotheses about the neurobiology of environmentally induced stereotypic behaviour.

[1] In the main manuscript, CSTC Circuits Hypotheses are discussed prior to the BG Pathways Hypotheses as this reflects the hierarchical structure of these hypotheses (i.e. each of the BG Pathways Hypotheses may be applied to each of the CSTC Circuits Hypotheses). Here, the anatomy and function of the basal ganglia pathways are explained first, as this information is necessary to understating the discussion of how the anatomy and function of the CSTC circuits regulate behaviour selection.

1. Pathways Within the Basal Ganglia

1.1. The 'classical/canonical' model of basal ganglia anatomy

The striatum (STR) is the main input structure of the basal ganglia. It receives glutamatergic (excitatory) projections from nearly all regions of the cortex (Wickens & Arbuthnott, 2010; Gerfen & Bolam, 2017), and has dorsal and ventral regions. In some animals (e.g. primates, carnivores, ungulates) the dorsal striatum is structurally divided into the dorsomedial caudate (Cn) and dorsolateral putamen (Pt) by the internal capsule, while in other animals (e.g. rodents) there is no clear division between these two regions (Reiner, 2010a). The ventral striatum contains the nucleus accumbens (NAc), which is structurally and functionally divided into a medial 'core' and out outer 'shell' (Meredith et al., 2008). The dorsal striatum receives dopaminergic projections from the substantia nigra pars compacta (SNc: the nigrostriatal pathway) while the ventral striatum receives dopaminergic projections from the ventral tegmental area[2] (VTA: the mesoaccumbens pathway) (Gerfen & Bolam, 2017). Importantly, these dopaminergic projections regulate the activity of the striatal projection neurons (for details see the Section 3.2. on dopamine).

The striatum is mainly comprised of GABAergic medium spiny neurons (MSN: approximately 95% of the neuron population in the striatum) which are the primary target of cortical input and the major projection neurons of the striatum (Oorschot, 2010; Plenz & Wickens, 2010; Gerfen & Bolam, 2017). Cholinergic and GABAergic interneurons (i.e. neurons that do not project outside of the striatum) make up the rest of the striatum, synapsing on MSNs and modulating their activity (Goldberg & Wilson, 2010; Tepper & Koós, 2010). Striatal cells are compartmentally organized by physical

[2] The VTA also sends dopaminergic projections to the frontal cortex (the mesocortical pathway), amygdala and hippocampus (the mesolimbic pathway) (Gerfen & Bolam, 2017). Along with the striatal dopaminergic projections, these too are important to consider when thinking about the hypotheses for environmentally induced stereotypic behaviours (SBs).

'borders' of interneurons (Gerfen, 1984; Walker et al., 1993; Kincaid & Wilson, 1996; Fujiyama et al., 2011) separating interconnected striosome 'patches'[3] (covering approximately 15% of the volume of the striatum: Johnston et al., 1990) embedded in an extra-striosomal matrix (Herkenham & Pert, 1981; Gerfen, 1984; Graybiel, 1990).

The striatal projection neurons relay to the basal ganglia output nuclei, the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNr), via two GABAergic (inhibitory) pathways: the striatonigral 'direct pathway' and the striatopallidal 'indirect pathway'. These neurons are intermingled in roughly equal numbers throughout the striatum (Gerfen & Bolam, 2017), and can be identified by their unique expression of neuropeptides and dopamine receptor types: striatonigral neurons selectively express the neuropeptide dynorphin, substance P, and D1-type dopamine receptors, while striatopallidal neurons selectively express the neuropeptide enkephalin and D2-type dopamine receptors (see also Sections 3.2. on dopamine and 3.3. on opioids). This reveals a slight predominance of striatonigral neurons in some striosome patches, and equal numbers of striatonigral and striatopallidal neurons in the matrix (Crittenden et al., 2011), but both striosome and matrix compartments project to the basal ganglia output nuclei (e.g. Gerfen & Young, 1988; Fujiyama et al., 2011).

[3] Canales and Graybiel (2000) and Saka and colleagues (2004) found that stereotypic responses to drugs of abuse are correlated with increased immediate early gene expression (used to index neuronal activity) in the striosome relative to matrix of the dorsolateral striatum. At first, this striosome-to-matrix activity imbalance was interpretated as being the cause of drug-induced stereotypic behaviours (SBs). However, the Graybiel lab has since reinterpreted based on studies that suggest increased striosome to matrix activity is *not directly causal* in drug induced SBs (for review see Crittenden et al., 2011). Rather, they now hypothesise that a striosome to matrix imbalance is related to hyper-responsivity to psychostimulants that predisposes individuals to drug-induced SBs (Crittenden et al., 2011).

Striatonigral neurons synapse directly on GPi/SNr neurons (some projecting to the GPi only, some to the SNr only, and some to both: Gerfen & Bolam, 2017) forming the direct pathway. Striatopallidal neurons project to the external segment of the globus pallidus (GPe) (Chang et al., 1981) and the GABAergic neurons in the GPe project to the subthalamic nucleus (STN), which provides glutamatergic input to the basal ganglia output nuclei completing the indirect pathway. The STN also receives glutamatergic cortical input, which forms the 'hyperdirect pathway' to the basal ganglia output nuclei. Each of these pathways are depicted in Figure S1. The GPi/SNr send GABAergic output to various brain regions (e.g. midbrain, hypothalamus, and cerebellum: Gerfen & Bolam, 2017), but of main interest to hypotheses pertaining to stereotypic behaviour are the glutamatergic cortical relay nuclei of the thalamus.

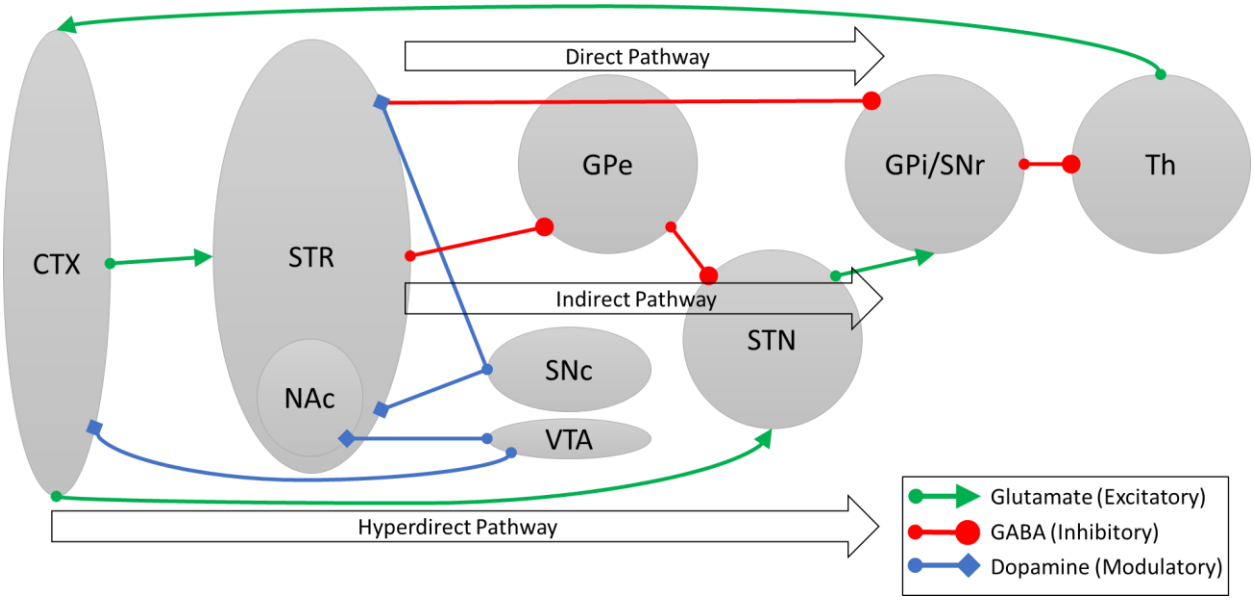

Figure S1. The 'classical/canonical' model of the basal ganglia circuitry based on the description in Gerfen & Bolam, (2017). Note that this figure is not to scale, and the relative location of each nucleus in this figure does not necessarily represent its precise anatomical location. From top to bottom: the direct pathway consists of monosynaptic GABAergic projections from the striatum to the output nuclei (GPi/SNr). The indirect pathway is multisynaptic, consisting of GABAergic projections first from the STR to GPe then from the GPe to the STN, and finally glutamatergic projections from the STN to the output nuclei. The hyperdirect pathway is monosynaptic, with glutamatergic projections from the cortex (CTX) to the STN. Although not depicted here (for simplicity), the direct and indirect pathways also emerge from the ventral striatum/NAc. The output nuclei regulate thalamic (Th) activity, which sends glutamatergic projections back to the cortex. The 'classical/canonical' dopaminergic connections of the basal ganglia are also depicted.

1.2. The basal ganglia pathways and behaviour selection

The ‘classical/canonical’ model of basal ganglia connectivity described above has informed much of our current understanding of basal ganglia function. It is thought that the basal ganglia pathways provide the circuitry (i.e. the means) for the cortex to ‘select’ behaviours (Mink, 1996; Redgrave et al., 1999; Gurney et al., 2001a, 2001b). Essentially, complex cortical information is integrated and filtered (see Section 2.3. on corticostriatal regulation of behaviour selection for more detail on this integration/filtration process) through the basal ganglia pathways where potential behaviours can either be ‘activated’ or ‘suppressed’. The classic and still widely accepted understanding is that activation of the direct and indirect pathways have opposing effects on behaviour selection: the direct pathway activates behaviours, while the indirect pathway suppresses them (Albin, et al., 1989; Delong, 1990). To do this, the direct pathway inhibits the basal ganglia output nuclei, while the indirect pathway disinhibits the basal ganglia output nuclei, which subsequently disinhibits and inhibits thalamo-cortical activity respectively (Lee et al., 2016; Bernal-Casas et al., 2017; Simonyan, 2019). Additionally, it is now understood that cortical activation of the hyperdirect pathway excites the output nuclei of the basal ganglia via the STN, which also increases inhibition on the thalamus, and is thought to serve as a ‘global stop signal’ that interrupts ongoing behaviour (Nambu et al., 2000; Nambu, et al., 2002; Aron & Poldrack, 2006).

This model is supported by recent optogenetic experiments in which selective activation of striatopallidal neurons suppresses locomotion and selective activation of striatonigral neurons increases locomotion (Kravitz et al., 2010). Likewise, optogenetic stimulation of striatonigral neurons increases the likelihood that an instrumental behaviour will be ‘chosen’ and striatopallidal activation decreases the likelihood of ‘choosing’ that behaviour (Kravitz et al., 2012). However, *both* the direct and indirect pathways are activated during behaviour initiation (e.g. Cui et al., 2013; Oldenburg et al., 2015) suggesting that their opposing effects on thalamic (and ultimately cortical) activity allow for selection/activation of certain ‘chosen’ behaviours via the direct

pathway while *simultaneously* suppressing competing/unwanted behaviours via the indirect pathway (Mink, 2003). Furthermore, optogenetic stimulation of striatonigral and striatopallidal MSNs may result in *both* excitation and inhibition of basal ganglia output for *each* pathway (Freeze et al., 2013). Still, striatonigral stimulation produces movement initiation which correlates selectively with inhibited SNr neurons, while striatopallidal stimulation and motor suppression is *selectively* related to excited SNr neurons (Freeze et al., 2013). In sum, it seems the functions of the direct and indirect pathways are generally understood, though the mechanisms behind them are much more complex than we originally thought.

1.3. The 'contemporary' model of basal ganglia anatomy

The 'contemporary' model of basal ganglia connectivity is more up-to-date and anatomically correct than the 'classical/canonical' model. Although this anatomy has not yet fully informed or fully modified our understanding of basal ganglia function, many authors are now highlighting these historically ignored more complex connections. Here we therefore briefly outline some of the major recent modifications to the classical model. For more comprehensive reviews and discussion of our changing understanding of basal ganglia anatomy, function, and involvement in pathology, please see: Calabresi et al., (2014); Nelson & Kreitzer (2014); Eisinger et al. (2018, 2019); Macpherson & Hikida (2019); and Simonyan (2019).

The 'contemporary' model of the basal ganglia builds on and modifies the 'classical' model with the addition of some extra pathways (and additional complexity, depicted in Figure S2). There are two "new" major pathways: the 'direct indirect pathway' (so named by Wilson, 2017) in which GPe axons (i.e. the same ones as in the indirect pathway) project *directly* to the GPi, and the 'recursively indirect pathway' which allows feedback from the STN to the GPe (e.g. Terman et al., 2002; Gittis et al., 2014). Precisely how these newly recognized pathways affect thalamic inhibition/disinhibition and consequently behaviour selection, is still not fully understood/integrated into our 'classical/canonical' conception (Gerfen & Bolam, 2017). Nevertheless, they do indicate

that previous views were simplistic. Our current understanding of the separate and opposing functions of the direct and indirect pathways is further complicated by the fact that they are not entirely anatomically independent. For one, striatopallidal and striatonigral neurons are connected by their own local axon collaterals (additional axonal branches off the main projection axon: Wilson & Groves, 1980; Bishop et al., 1982), which may competitively and/or cooperatively modulate the functional balance between the direct and indirect pathways (Plenz, 2003). Furthermore, striatonigral neurons in the dorsal striatum have axon collaterals projecting to the GPe (Kawaguchi et al., 1990), thereby 'bridging' the direct and indirect pathways (a.k.a. 'bridging collaterals': Gerfen & Bolam, 2017; Wilson, 2017) thus, most striatonigral neurons (about 60%: Cazorla et al., 2014) are not purely 'direct pathway' neurons. These collaterals mean there is potential for the direct pathway to modulate the indirect pathway at the level of the GPe (Calabresi et al., 2014; Cazorla et al., 2014). Likewise, in the ventral striatum, 'direct pathway' neurons project not only to the SNr, but also to the ventral pallidum (VP)[4], the sole target of 'indirect pathway' neurons (Kupchik et al., 2015).

The contemporary model also recognizes other intra-basal ganglia connections long known of but previously largely ignored (Wilson, 2017). These include various feedback pathways likely important for regulating the pathways' activity. GABAergic neurons in the GPe project back to the striatum where they target GABAergic interneurons and MSNs (Gerfen & Bolam, 2017; Kita & Jaeger, 2017; Wilson, 2017). The STN, and the midline and intralaminar nuclei of the thalamus, also project back to the striatum via glutamatergic afferents (Kita & Kitai, 1987; Mallet et al., 2012; Haber, 2017). The STN also sends glutamatergic projections to the SNc (Smith & Grace, 1992), putting the hyperdirect and indirect pathways in a potential position of control over nigrostriatal dopamine release. The striatum can also regulate its dopamine

[4] This has led some authors to suggest that the concepts of the 'direct' and 'indirect' pathways can not/should not be applied to the ventral striatum. However, by the same notion, this argument could also be applied to the dorsal striatum.

concentration through reciprocal connections with the SNc and VTA (Haber, 2017). Furthermore, dopaminergic neurons in the SNc can enhance GABAergic output of the SNr, in what has been deemed an 'ultra-short pathway' (Zhou et al., 2009). In sum, these two additional pathways, evidence of greater connectivity between the direct and indirect pathway, and feed-back rather than purely feed-forward processing, all show that the regulation of behaviour selection by balancing the excitation and inhibition of thalamic relay nuclei is likely much more complex than the 'classical/canonical' model suggests.

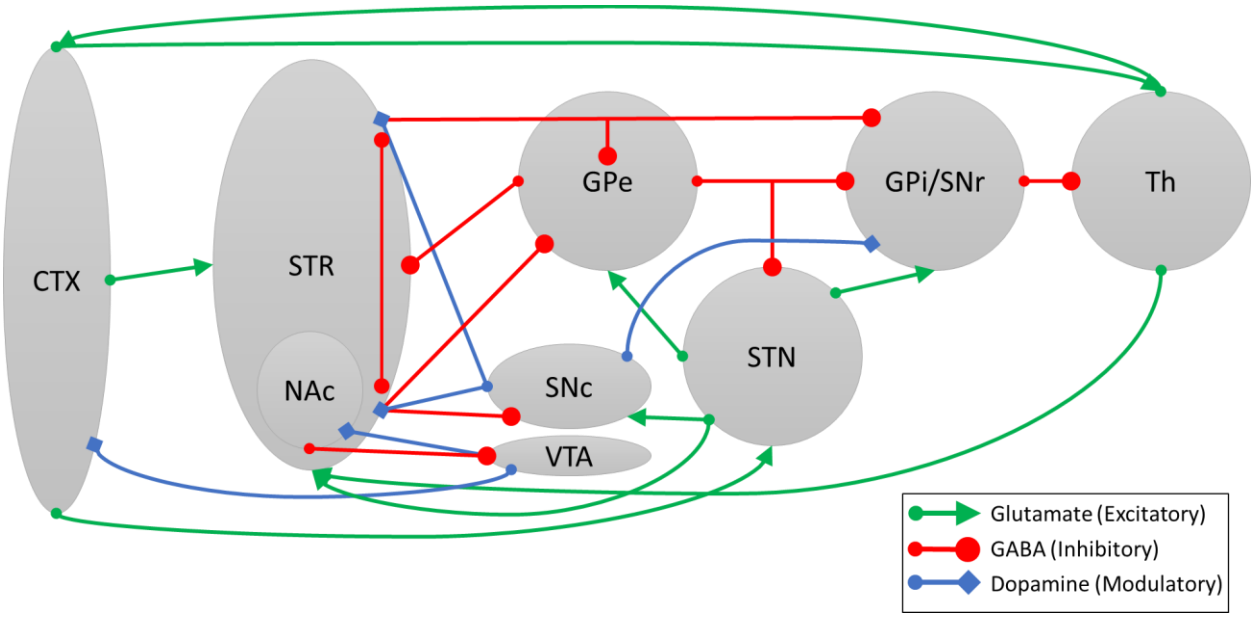

Figure S2. The contemporary model of the basal ganglia circuitry based on descriptions by Gerfen & Bolam (2017) and Wilson (2017). Note the bridging collaterals between the striatonigral and striatopallidal neurons in the striatum, and the axon collaterals of the striatonigral neurons which bridge the direct pathway with the indirect pathway. Also, note the direct projections from the GPe to the GPi/SNr for the 'direct indirect pathway' and the collaterals projecting to the STN, which project back to the GPe forming the 'recursively indirect pathway'.

2. Cortico-Striatal-Thalamo-Cortical Circuits

The basal ganglia are reciprocally connected to the frontal cortex through multiple cortico-striatal-thalamo-cortical circuits (CSTC): the 'sensorimotor', 'cognitive/associative' and 'emotion/motivation/limbic' circuits named for the functionally related, though anatomically distinct, cortical regions they originate from and return to (Alexander et al., 1986; Parent & Hazrati, 1995; Strick et al., 1995; Haber et al., 2000). The CSTC circuits are topographically organized[5], maintaining their spatial relationship from the cortex as they travel to the striatum and then (roughly in parallel) through the basal ganglia and to the thalamus (Groenewegen et al., 2017; Haber, 2017). This organization essentially creates different functional domains[6] within the striatum and subsequent basal ganglia nuclei (e.g. the GP and STN also have sensorimotor, cognitive/associative, and emotion/motivation/limbic domains: Francois, 2004; Karachi et al., 2005; Winter et al., 2008). In addition to their topographic/functional organization, the CSTC circuits have extensive overlaps in projections that cross functional domains (Groenewegen et al., 2017; Haber, 2017). Here we describe the general cortical, striatal, and thalamic regions belonging to each functional circuit. We focus our description on frontal projections to the functional domains of the striatum and bring attention to the areas of convergence in the rodent cortico-striatal system, as this is most relevant to the research conducted on environmentally induced stereotypic behaviours so far. For a precise description of these circuits including their segregation, overlap, and integration with thalamo-striatal projections in primates see Haber (2017).

---

[5] The sensorimotor circuit is also somatotopically organized, with each body part having its own microcircuit. Thus, the sensorimotor circuit is sometimes further divided into a 'skeletomotor' circuit (for the head and body) and 'oculomotor' circuit (for the muscles of the eyes).

[6] Some functionally related areas of the cortex are highly interconnected, forming "edges" that likely send "mixed" signals to the striatum, thus blurring functional boundaries (Groenewegen et al., 2017; Haber, 2017). Furthermore, as basal ganglia regions get progressively smaller (from input to output structures), there is thought to be a greater degree of convergent processing via overlap of functional domains (Haber, 2017).

In both primates and rodents, the cortico-striatal system is organized in a ventromedial-to-dorsolateral topography along the rostrocaudal axis: the most ventral regions of the cortex project ventromedially while progressively more dorsal cortical regions project dorsolaterally (Voorn et al., 2004). The ventral striatum (i.e. NAc) receives limbic (including hippocampus and amygdala), prefrontal, and orbitofrontal projections; the dorsomedial striatum (DMS) (also caudate nucleus, with some overlap to the putamen, in species with structural separation: Künzle, 1975) receives input from prefrontal, orbitofrontal, and parietal and temporal association cortices; the dorsolateral striatum (DLS) (or putamen in species with structural separation: Künzle, 1975) receives motor and somatosensory projections (Gerfen & Bolam, 2017; Groenewegen et al., 2017; Haber, 2017). Accordingly, these striatal regions (and their subsequent basal ganglia regions) are simply referred to as the 'emotion/motivation/limbic', 'cognitive/associative' and 'sensorimotor' functional domains respectively. The cortico-striatal afferents have dense 'focal' projections, highly targeted to a specific striatal domain, and extended 'diffuse' projections that occupy a large proportion of striatal volume and reach beyond the focal domain overlapping with projections from other areas (Haber et al., 2006; Calzavara et al., 2007; Wickens & Arbuthnott, 2010; Mailly et al., 2013). The topography of projections from the striatum through the basal ganglia are maintained as they travel to the thalamo-cortical relay nuclei: the mediodorsal (MD), ventral anterior (VA) and MD, and ventrolateral (VL) nuclei of the thalamus for the emotional/motivational/limbic, cognitive/associative, and sensorimotor, circuits respectively (Gerfen & Bolam, 2017; Haber, 2017) (see Figure S3). This topographic/functional organization appears to follow the same general pattern in rodents and primates, though the cortical regions of origin (and return) are slightly different in rodents because they have a smaller and less complex cortex (Gerfen & Bolam, 2017).

In rodents, the medial portion of the NAc (or VMS) receives dense focal projections from the infralimbic (IL) and prelimbic (PrL) cortices, and more diffuse projections from the dorsal anterior cingulate cortex (dACC), and medial orbital (MO) and ventral orbital (VO) cortices (Mailly et al., 2013). The dorsolateral orbital (DLO)

cortex, the dACC, and the PrL densely project to the lateral portion of the NAc (or VLS) which also receives diffuse projections from the MO and VO cortices (Mailly et al., 2013). The DMS receives dense input from the ventrolateral orbital cortex (VLO), the ventral anterior cingulate cortex (vACC), PrL, MO, and VO cortices with a mix of diffuse and focal projections (which are more centralized in the dorsal striatum) from the dACC (Mailly et al., 2013). Lastly, the DLS primarily receives projections from the motor cortices (primary: M1, secondary: M2) (Mailly et al., 2013). See Figure S3 for the circuits described above. For a precise description of these circuits see Mailly et al., (2013) (on Norway rats [*Rattus norvegicus*]). Cortico-striatal mapping in mice (*Mus musculus*) demonstrates similarities to rat topography (Pan et al., 2010; Wall et al., 2013; Ullmann et al., 2014; Guo et al., 2015; Hintiryan et al., 2016; Hunnicutt et al., 2016).

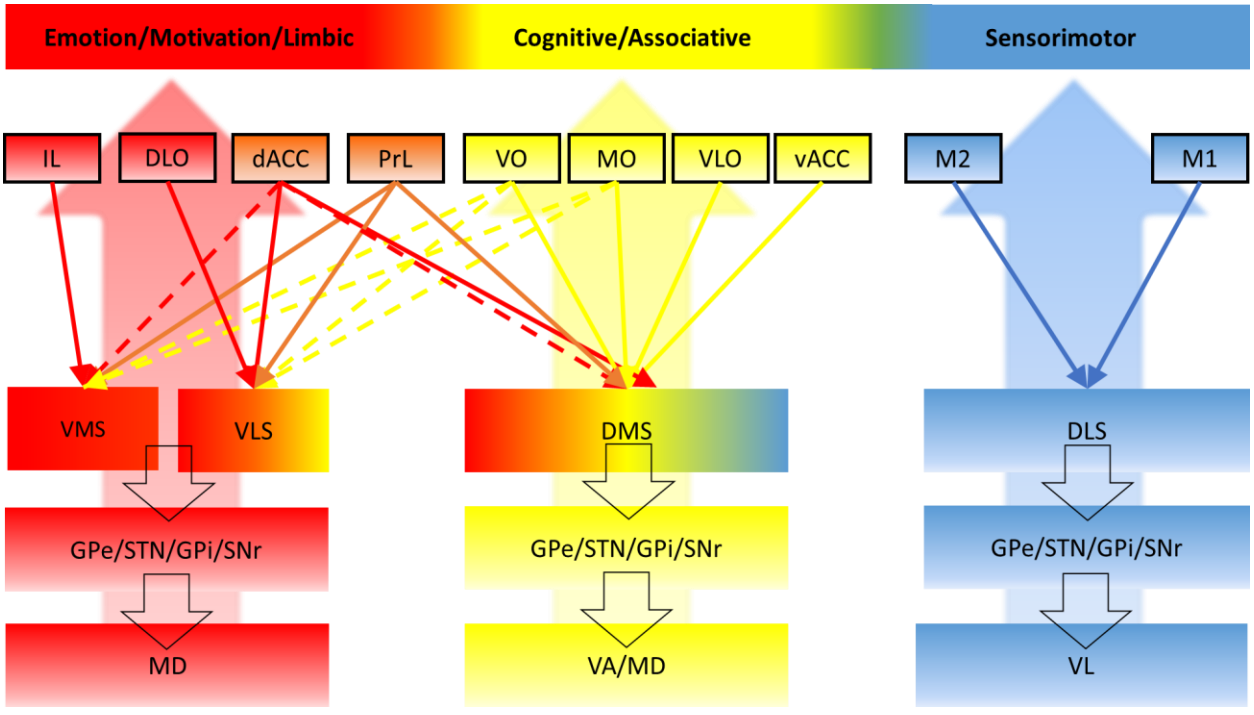

Figure S3. The cortico-striatal-thalamo-cortical circuits in rodents, based on descriptions by Groenewegen et al. (2017) and Haber (2017). Solid arrows from prefrontal regions indicate focal projections, while dashed arrows indicate diffuse projections. For a precise anatomical depiction of the prefrontal projections to the striatum see Mailly et al. (2013).

As illustrated above (in Figure S3), there is some degree of overlap in both focal and diffuse projections as they cross functional domains (Groenewegen et al., 2017; Haber, 2017). This overlap allows for the convergence of inputs, and integration of motor, cognitive, and emotional/motivational information from cortical, limbic and thalamic inputs (Groenewegen et al., 2017; Haber, 2017). Striatal areas of overlap are mostly made up of projections from adjacent, interconnected cortical areas that exchange cortico-cortical information and likely send 'mixed' signals to the striatum and STN (Calzavara et al., 2007; Haber & Calzavara, 2009; Mailly et al., 2013). Additionally, thalamic relay neurons also target cortical regions other than the source of input for a specific functional circuit, this also provides a cross-flow of information between cortical regions (Haber et al., 2000). Thus, while the basal ganglia maintain the specific functional aspects of each circuit through the largely parallel organization, organizational overlap also allows for cross-talk and integration between the CSTC circuits (Gerfen & Bolam, 2017; Haber, 2017).

2.1. Anatomy of cortico-striatal projections

Cortico-striatal input comes mainly from layer V (plus layer III and VI: Wickens & Arbuthnott, 2010) pyramidal glutamatergic neurons, of nearly all areas of the neocortex (Gerfen & Bolam, 2017), though GABAergic projections from the auditory and motor cortices have also been identified (Rock et al., 2016). There are two main types of cortico-striatal projection neuron: 1) intratelencephalic (IT) which have axon collaterals within the striatum and cortex (Reiner, 2010b; Wickens & Arbuthnott, 2010) and 2) corticofugal (i.e. projecting to the brainstem or spinal cord) pyramidal tract (PT) neurons located mainly in frontal cortex from which a striatal projection collateral arises from the descending axon (Wickens & Arbuthnott, 2010). PT neurons also project to striatum, thalamus, STN, GPi/SNr, as different populations of neurons projecting to different regions, and as individual neurons providing the same information to multiple regions (Reiner, 2010b; Kita & Kita, 2012; Gerfen & Bolam, 2017). All corticostriatal neurons have collaterals in other brain regions: none project exclusively from the cortex to the striatum (Wickens & Arbuthnott, 2010).

While individual MSNs receive projections from both IT and PT type neurons (Wickens & Arbuthnott, 2010) (and likewise, both the striosome and matrix receive both IT- and PT- type projections: Gerfen and Bolam, 2017), it is unclear whether striatonigral and striatopallidal neurons receive projections from both types equally (e.g. Kress et al., 2013), or whether instead they are differentially targeted (e.g. Lei et al., 2004). Likewise, while cortical afferents to a single MSN arise from both functionally related and functionally *different* cortical areas (Cowan & Wilson, 1994; Ramanathan et al., 2002), it has also been suggested that striatonigral and striatopallidal MSNs are specifically targeted by different functional areas (e.g. limbic areas preferentially targeting striatonigral neurons, and motor areas preferentially targeting striatopallidal neurons) (Wall et al., 2013). Thus precisely how the cortex controls basal ganglia pathway activation (whether through one channel or multiple channels) remains to be determined.

2.2. Anatomy of thalamo-cortical projections

As mentioned earlier, projections from the thalamic relay nuclei (i.e. VL [sensorimotor circuit], MD [associative/cognitive circuit], and VA [limbic circuit]) terminating in layer V of their cortical area of origin, ‘end’ the cortico-striatal-thalamo-cortical reciprocal circuits and sustain functionally segregated processing through the cortico-basal ganglia processing system (Alexander et al., 1986; Parent & Hazrati, 1995). However, the thalamus is not just a simple relay station (see Sherman, 2016). Much like the striatum, the thalamus also serves as an integration center between functional circuits, doing so through non-reciprocal cortico-thalamic projections and thalamic projections to different cortical layers (Haber, 2017).

The thalamic relay nuclei also receive extensive projections from the cortex, some from their own cortical targets (e.g. Colwell, 1975; White & Deamicis, 1977), creating reciprocal thalamo-cortico-thalamic circuits, and some from cortical areas not innervated by the receiving thalamic relay nucleus (e.g. Deschenes et al., 1998; Rouiller & Welker, 2001) creating non-reciprocal cortico-thalamic pathways (Haber, 2017). The

reciprocal cortico-thalamic connections potentially aid in goal-directed behaviour (e.g. Alcaraz et al., 2018) and are thought to “reinforce” the parallel function processing of the CSTC circuits (McFarland & Haber, 2002) and/or provide the means for “feedback” on CSTC processing[7] (Haber, 2017). The non-reciprocal cortico-thalamic connections[8], on the other hand, provide the means for “feed-forward” distribution of cortical information via the thalamus (Rouiller & Welker, 2001) and integration of cortical information across functional circuits (McFarland & Haber, 2002; Haber & Calzavara, 2009; Haber, 2017).

Integrative processing in the cortico-basal ganglia system is further accomplished through thalamo-cortical projections to different layers of the cortex (Haber & Calzavara, 2009; Haber, 2017). Projections from the thalamic relay nuclei also terminate in the superficial (layers I/II) and middle (layers III/IV) layers of the cortex (Harvey, 1980; Hersch & White, 1981; White & Hersch, 1982; McFarland & Haber, 2002). Projections to the superficial layers (where adjacent cortical regions are interconnected) can modulate cortico-cortical functional connectivity (e.g. Schmitt et al., 2017) and thus may facilitate cross communication between functional CSTC circuits (Haber & Calzavara, 2009; Haber, 2017). Furthermore, projections to superficial layers provide the means to “train” cortico-cortical associations via the basal ganglia as part of habit formation (Hélie et al., 2015).

[7] In this sense, Haber (2017) emphasizes the importance of considering processing in the cortical-basal ganglia behaviour selection system as starting in the cortex through the striatum, basal ganglia nuclei, and back to the cortex via the thalamus, but not operating in reverse.

[8] In primates, the non-reciprocal cortico-thalamic projections are organized such that they would seem to support information flow from association areas of the cortex to primary motor areas, thus following a similar pattern of integration to that described for the striatum (McFarland & Haber, 2002; Haber, 2017). However, it is not clear to what extent this organization applies to other mammals.

2.3. Corticostriatal regulation of behaviour selection

So how do the CSTC circuits affect basal ganglia pathway activation and behaviour selection? Behaviour selection is thought to depend on striatal integration of sensorimotor, cognitive/associative, and emotional/motivational information. For instance, the emotion/motivation/limbic ventral striatum and the cognitive/associative DMS affect sensorimotor information in the DLS through convergent terminal fields in a ventral-to-dorsal striatal organization (Haber, 2017): emotions and motivations determine the goal and drive the behaviour, cognition and associative information are used for planning the appropriate strategy to obtain that goal, and sensorimotor processing prepares and executes the correct movements (Haber, 2003). This ventral-to-dorsal integration of striatal information is thought to be supported by an upwardly 'spiraling', non-reciprocal striato-nigro-striatal dopamine pathway (Haber et al., 2000). There is also a striosomal limbic network (the striosome receiving mainly limbic projections: Jimenez-Castellanos & Graybiel, 1987; Gerfen, 1989; Eblen & Graybiel, 1995; Kincaid & Wilson, 1996) embedded in the cognitive/associative and sensorimotor domains of the striatum (Graybiel, 2008). This network contains the only striatal neurons with direct projections to the SNc (e.g. Gerfen, 1984; Fujiyama et al., 2011). Both of these ventral-/limbic-originating striatal dopamine pathways are thus in a prime position to modulate basal ganglia pathway activity (see Section 3.2. on dopamine) of the dorsal/motor striatum (Crittenden et al., 2011), ultimately influencing behaviour selection. Thus, the cortico-basal ganglia system is thought to guide behaviour selection through *both* parallel *and* integrative processing of emotional cognitive, and sensorimotor information, all influencing a common output pathway (e.g. Redgrave et al., 1999).

Although it is still largely unknown precisely how cortico-striatal inputs regulate behaviour selection via activation of the basal ganglia pathways, some hypotheses have been advanced. For one, striatal MSNs are thought to require convergent stimulation from multiple cortical inputs, carrying information about the external environment, reward prediction, and planned behaviours, to activate (Reiner, 2010b). This is because

thousands of excitatory glutamatergic cortical inputs converge (primarily on dendritic spines) on a single striatal MSN (Reiner, 2010b; Gerfen & Bolam, 2017). Few inputs come from a single cortical projection neuron; instead, inputs come from many different cortical neurons from both functionally related and functionally different cortical areas (Cowan & Wilson, 1994; Ramanathan et al., 2002). Accordingly, postsynaptic activation of striatal MSNs, which have low membrane excitability, is dependent on convergent cortical input resulting in the temporal summation of excitatory postsynaptic potentials (Wilson, 1995). Striatonigral neurons in particular, which are less excitable than striatopallidal neurons (Feltz & Albe-Fessard, 1972), may require substantial cortical input to overcome their thresholds for activation. This is thought to serve yet another integrative process, in that only the most appropriate behaviours (given current motivational state and learned associations between external stimuli, behaviour, and reward) are activated in the striatum (Reiner, 2010b). But how are behaviours represented in the striatum?

In addition to the above hypothesis, only certain combinations of cortical inputs are thought able to excite striatal MSNs (Wickens & Arbuthnott, 2010), and the pattern of this convergent activation 'encodes' the type of cortical information being transmitted (Gerfen & Bolam, 2017). Essentially, because the set of inputs to each MSN is unique, with no two MSNs sharing the same cortical inputs (Gerfen & Bolam, 2017), striatal MSNs are thought to encode specific patterns of cortical activity, and whether an MSN is excited depends on the activity of its specific cortical connections (i.e. the set of inputs that fire one MSN could not activate another) (Wilson, 2000; Wickens & Arbuthnott, 2010). According to this model (the 'combinatorial selection model'), striatal MSNs must be activated in groups, such that different 'ensembles' of MSNs encode a different situation and/or behaviour such that the output/behaviour selected reflects the combination of MSNs that are activated together (Wickens & Arbuthnott, 2010). Then, changing the strength of input to certain MSNs within an ensemble (e.g. by various plasticity mechanisms like long-term potentiation [LTP], long-term depression [LTD] and dendritic arborization), assuming a single MSN is part of multiple ensembles, should allow a different ensemble to be selected. Such changes have been hypothesized to

serve a ‘filtering’ effect in the behaviour selection process, such that only the strongest striatal inputs are relayed to the GPe and GPi/SNr, while weaker signals are ‘filtered out’ (e.g. Bamford et al., 2004).

3. Important Neurochemicals in the Basal Ganglia

3.1. Glutamate

Glutamatergic input from the cortex and thalamus directly regulates striatal MSN activity, and thus basal ganglia pathway activation, through ionotropic and metabotropic glutamate receptors. Glutamate acts as an excitatory neurotransmitter at AMPA receptors where fast, depolarizing, excitatory post synaptic potentials (ESPS) are produced when the AMPA ion channel opens and K^+ and Na^+ flow into the cell (e.g. Calabresi et al., 1996). On the other hand, NMDA receptors contribute to depolarization and LTP via the opening of their Ca^{2+} channels when glutamatergic input is much stronger and produces sufficient depolarization to dislodge the Mg+ blocking the ion channel (Kerr & Plenz, 2002; Pomata et al., 2008). The striatum is also densely packed with all three groups of metabotropic glutamate receptors (mGLuR) (Martin & Blackstone, 1992; Shigemoto et al., 1993). Group I receptors (mGluRs 1 & 5) are coupled to G_q proteins which activate the phospholipase C → Ca2+ → PKC signaling cascade and increase NMDA-R activity (e.g. Skeberdis et al., 2001) group II (mGluRs 2 & 3) and group III receptors (mGluRs 4-8) are coupled to $G_{i/o}$ proteins, inhibiting the AC → cAMP → PKA cascade and decrease NMDA-R activity (e.g. Ambrosini et al., 1995). While Group I mGluRs are mainly postsynaptic, Groups II and III are mainly presynaptic (e.g. Shigemoto et al., 1997).

Striatal MSNs are biphasic, exhibiting either persistent stable depolarization (a.k.a. “up-state”) or negative resting membrane potentials (a.k.a. “down-state”) (Plenz & Wickens, 2010). These states regulate both acute activation of striatal MSNs by glutamate, and synaptic plasticity mechanisms. Regarding acute activation, MSN down-states prevent action potentials from occurring, making striatal MSNs largely

unresponsive to low levels of glutamatergic input (Wickens & Wilson, 1998; Plenz & Wickens, 2010). A transition to the up-state is triggered and maintained by high levels of glutamatergic input (e.g. Wilson & Kawaguchi, 1996), likely from many corticostriatal neurons in close temporal proximity, making the MSN up-state tightly correlated with cortical activity (O'Donnell, 2010). It is in the up-state, but not the down-state, that action potentials can be produced. But up-states alone do not produce action potentials, further depolarization during the upstate is still required (Wickens & Wilson, 1998; Plenz & Wickens, 2010). Unlike the generation of action potentials, synaptic plasticity mechanisms can be activated during both down-states and up-states. Persistent, and sufficient, activation of corticostriatal synapses occurring during up-states causes LTP through NMDA-R activation, while the same level of stimulation occurring during down states will result in LTD through mGlu1/5-R activation (Di Filippo et al., 2010).

In the striatum, NMDA receptors are required for spike-timing dependent plasticity (STDP: Hebbian plasticity) which provides a 'temporal evaluation' of corticostriatal input (Plenz & Wickens, 2010) by specifically enhancing (through LTP) cortical inputs that directly contribute to MSN firing (i.e. those that occur before post-synaptic potentials: e.g. Sjöström & Nelson, 2002), and by down-regulating (through LTD) cortical inputs that do not directly cause depolarization (i.e. those that occur *after* the MSN action potential: e.g. Sjöström & Nelson, 2002). This applies to both striatonigral and striatopallidal MSNs (e.g. Shen et al., 2008). Importantly, dopamine can modulate the direction (i.e. LTP or LTD) of change during STDP (e.g. Pawlak & Kerr, 2008), but is not necessary for the induction of LTD or LTP (i.e. both can occur in the absence of dopamine: Surmeier et al., 2010).

3.2. Dopamine

Striatal dopamine (DA) serves a neuromodulatory role, having both excitatory and inhibitory effects depending on the type of dopamine receptor it binds to. Striatonigral MSNs selectively express D1 type dopamine receptors (D1DR), and at high levels (Gerfen et al., 1990; Surmeier et al., 1996). These are coupled to stimulatory G-proteins and increase MSN excitability[9] (Keefe & Horner, 2010; Surmeier et al., 2010; Plenz & Wickens, 2017). Striatopallidal MSNs instead selectively express D2 type dopamine receptors (D2DRs) (Gerfen et al., 1990; Surmeier et al., 1996), which are coupled to inhibitory G-proteins and decrease MSN excitability[10] (Keefe & Horner, 2010; Surmeier et al., 2010; Plenz & Wickens, 2017). Accordingly, the classical/canonical model of basal ganglia function predicts that D1DR activation increases output of the direct pathway (thus increasing behavioural activation), while D2D2 activation decreases output of the indirect pathway (thus increasing behavioural activation) (Albin et al.,1989; Delong, 1990).

However, the actual effects of dopamine on activity of the basal ganglia pathways/nuclei are not that straight forward, including changes in neuronal activity that are not predicted by the classical/canonical model (Walters & Bergstrom, 2010). First, independent activation of D2DRs only produces a small increase in GPe activity (i.e. disinhibition for the indirect pathway); instead, D1DR and D2DR co-activation is required to increase GPe activity (Walters & Bergstrom, 2010). Likewise, co-activation of D1DRs and D2DRs increases Fos expression (an immediate early gene commonly used as a marker for neuronal activity) in striatonigral neurons more than independent

[9] Dopamine binding at these receptors affects the conductance and trafficking of various ion channels (Plenz & Wickens, 2017), increases the expression of various genes (Keefe & Horner, 2010) and increases surface expression of AMPA and NMDA receptors (e.g. Snyder et al., 2000; Hallett et al., 2006).

[10] Dopamine binding here also affects the conductance and trafficking of various ion channels (Plenz & Wickens, 2017), and decreases the expression of various genes (Keefe & Horner, 2010), as well as decreasing AMPA-R induced post-synaptic currents (Surmeier et al., 2010) and reducing cortico-striatal glutamate release (though whether by pre-synaptic and/or post-synaptic activation is yet unknown: Bamford et al., 2004; Yin & Lovinger, 2006).

activation of D1DRs (Keefe & Horner, 2010). Second, co-activation of D1DRs and D2DRs produces a mix of increased, decreased, and no change in SNr activity as opposed to the predicted decrease in activity (Walters & Bergstrom, 2010). Finally, D2DR agonists do not affect STN activity, though they should increase it according to the classical/canonical model; instead, D1DR agonists increase STN activity (Walters & Bergstrom, 2010). Thus, the effects of dopamine on the basal ganglia pathways are not completely understood.

Nevertheless, dopamine is undoubtedly critical for many of the functions performed by the CSTC circuits, including behavioural selection/activation and switching (e.g. Redgrave et al., 1999), reward learning (e.g. Schultz, 1998) and the acquisition of new behavioural responses (e.g. Redgrave & Gurney, 2006). Dopamine exerts its modulatory role through its effects on neuroplasticity, paralleling its short-term effects on MSN excitability (Surmeier et al., 2010). Importantly, striatal dopamine plays a major modulatory role in corticostriatal plasticity, influencing the direction of change in synaptic strength (i.e. potentiation or depression). During peak dopamine signaling, the co-occurrence of pre (cortical)- and post (striatal)- synaptic excitatory potentials thus cause LTP in D1DR-expressing striatonigral (direct) neurons and LTD in D2DR-expressing striatopallidal (indirect) neurons (Shen et al., 2008; Reiner, 2010b; Surmeier et al., 2010; Wickens & Arbuthnott, 2010). This improves the efficacy of corticostriatal projections in activating the direct pathway and reduces their efficacy in activating the indirect pathway. During low levels of dopamine, in contrast, the opposite effect takes place: LTD occurs in striatonigral neurons and LTP occurs in striatopallidal neurons, making activation of the direct pathway more difficult and activation of the indirect pathway easier (Shen et al., 2008; Reiner, 2010b; Wickens & Arbuthnott, 2010). This effect of phasic dopamine release is thought to serve an important integrative function during convergence of sensory, contextual, and motor information in the striatum (Redgrave et al., 2010; cf. Section 2.3. on corticostriatal regulation of behaviour selection), by adjusting the relative sensitivities of MSNs. Essentially, these changes are thought to bias the behaviour selection system so that certain behaviours are more likely to be repeated than others (Redgrave et al., 2010; Surmeier et al., 2010).

3.2.1. Adenosine

The effects of striatal dopamine are further modulated by striatal adenosine. Striatopallidal neurons specifically express A_{2A} adenosine receptors (striatonigral neurons have negligible levels of A_{2A}: Schiffmann et al., 1991), particularly on dendritic spines at asymmetric synapses, where they modulate excitatory input: Morelli et al., 2010). A_{2A} adenosine receptors activate G_s/G_{olf} (stimulatory) proteins and antagonize the effects of D2DR stimulation (through opposite effects on the AC → cAMP → PKA cascade: Schulte & Fredholm, 2003), thus increasing neuron excitability[11]. A_1 adenosine receptors (coupled to Gi/Golf [inhibitory] G-proteins) are located post-synaptically in *both* striatonigral and striatopallidal neurons, where they reduce neuronal response to glutamatergic and dopaminergic inputs (Morelli et al., 2010). They are also located in the nerve terminals (i.e. pre-synaptically) in striatal dopaminergic nerve terminals, where they directly inhibit dopamine release in the striatum (Borycz et al., 2007). A_1 and A_{2A} receptor heteromeres on corticostriatal nerve terminals (Hillion et al., 2002) modulate glutamate release. When adenosine concentrations are low, and primarily A_1 receptors are stimulated, glutamate release is decreased; while adenosine concentrations are high and A_{2A} receptors are also stimulated, glutamate release is increased. Ultimately, the effect of dopamine on the direct and indirect pathway is thus dependent on adenosine.

[11] Striatopallidal neurons can also express LTP during peak dopamine signaling when A_{2A} receptors are also activated (Shen et al., 2008; Reiner, 2010; Surmeier et al., 2010; Wickens & Arbuthnott, 2010).

3.3. Opioids

Endogenous opioids (neuropeptides) act as neuromodulators in the basal ganglia. Striatonigral neurons which give rise to the direct pathway produce the opioid-peptide substance P and dynorphins (Vincent et al., 1982; Gerfen et al., 1988; Gerfen & Bolam, 2017). Furthermore, the striatopallidal neurons which begin the indirect pathway produce enkephalins and neurotensin (Voorn et al., 1999). All opioid receptors (κ-opioid receptors [KOR], μ-opioid receptors [MOR] and δ-opioid receptors [DOR]) are coupled to G_i or G_o (inhibitory G-proteins) and inhibit the AC → cAMP → PKA intracellular signaling cascade (Emson et al., 2010). Dynorphins bind primarily to KORs, but they also bind to MORs and DORs albeit with less affinity (Le Merrer et al., 2009). Enkephalins primarily bind to DORs, and, with less affinity, to MORs (β-endorphin binds with the greatest affinity to MORs), but do not bind at all to KORs (Le Merrer et al., 2009). All opioid receptors are widely expressed throughout the brain, but with elevated levels in the cortex, limbic system, and brainstem. Notably, within the basal ganglia, DORs and MORs are most abundant in the striatum, being found on both striatopallidal and striatonigral neurons (Emson et al., 2010). So how do these neuropeptides and their receptors modulate basal ganglia function and pathway activity? Here we summarize what is known about the effects of dynorphins on kappa-opioid receptors and enkephalins on mu, and delta-opioid receptors.

Endogenous opioids are thought to serve a neuroadaptive response, maintaining ‘system equilibrium’ of the direct and indirect pathways through modulation of the dopamine system (Steiner, 2010). For instance, chronic administration of dopamine agonists like cocaine, amphetamine and L-DOPA greatly increase the expression of dynorphin and substance P in striatonigral neurons, while enkephalin in striatopallidal neurons is greatly increased by chronic administration of D2DR antagonists and dopamine depletion (for review see Steiner & Gerfen, 1998). Thus, increased dynorphin transmission is thought to result from the chronic overactivation of striatonigral neurons caused by D1DR stimulation, while increased enkephalin transmission is thought to result from the chronic overactivation of striatopallidal neurons caused by decreased

D2DR mediated inhibition (Steiner & Gerfen, 1998). Essentially, the endogenous opioid system in the basal ganglia is thus thought to act as a counterbalance to the dopamine system, maintaining relative pathway activity through negative feedback when the dopamine system goes awry (Keefe & Horner, 2010; Steiner, 2010). Accordingly, any imbalance between the direct and indirect pathway activity will be reflected by altered striatal neuropeptide content (e.g. elevated enkephalin in Parkinson's disease: Gerfen et al., 1990)

Dynorphin release by striatonigral neurons, acting on KORs, can inhibit both dopamine (e.g. Di Chiara & Imperato, 1988) and glutamate (e.g. Gray et al., 1999) release in the striatum. Striatal dynorphin release can inhibit dopamine release by stimulating presynaptic KORs on dopamine nerve terminals (e.g. Mulder et al., 1984), or by acting on KORs on dopaminergic dendrites and cell bodies in the SNc (e.g. Reid et al., 1988). Likewise, dynorphin can inhibit glutamate release by activating KORs on corticostriatal nerve terminals (e.g. Gray et al., 1999). Additionally, dynorphin can reduce striatonigral responses to dopamine, through kappa-opioid auto-receptors that inhibit the post-synaptic effects of D1DR activation (e.g. Steiner & Gerfen, 1996). Thus, dynorphin acts as a negative feedback mechanism when striatonigral activity is elevated, working to reduce further activation caused by elevated dopamine so as to restore normal activity of the direct pathway.

Enkephalin serves a similar negative feedback function, inhibiting striatopallidal activity when the indirect pathway is over-active. Activation of MORs and DORs in the striatum inhibits glutamate-induced immediate early gene expression, and D2DR antagonist induced gene expression (a way to simulate loss of dopamine activity; e.g. Steiner & Gerfen, 1999). In contrast, activation of DORs and MORs in the SNc increases dopamine release by hyperpolarizing GABAergic interneurons, thus reducing their inhibitory influence on dopaminergic neurons (e.g. Kalivas & Stewart, 1991; Schad et al., 1996). Additionally, enkephalin can inhibit corticostriatal glutamate release by increasing acetylcholine release in striatal interneurons (e.g. Mulder et al., 1984; Rawls & McGinty, 2000) and inhibit GABA release from striatopallidal terminals by acting on

auto-receptors (e.g. Maneuf et al., 1994). Thus, all these actions of enkephalin may help decrease indirect pathway activity, providing a compensatory mechanism for diminished dopaminergic activity.

3.4. Serotonin

The basal ganglia receive serotonergic innervation mainly from the dorsal raphe nucleus (DRN) (Gerfen & Bolam, 2017). Cumulatively, the basal ganglia nuclei possess all seven types of serotonin (5-HT) receptors, with different receptor types being expressed in different nuclei and cells (Emson et al., 2010). All 5-HT receptors are G-protein coupled receptors, except for 5-HT3 (e.g. found on striatonigral and striatopallidal projection neurons and cholinergic interneurons in the striatum: Emson et al., 2010) which is a ligand-gated cation channel, permeable to Na^+ and K^+. The 5-HT4 receptor (on dopaminergic projection neurons in the SNc: Emson et al., 2010), 5-HT6 receptor (e.g. on dendrites of striatopallidal and striatonigral projection neurons: Di Matteo et al., 2008), and 5-HT7 receptor (e.g. found in the NAc: Di Matteo et al., 2008), are all coupled to G_s, activating the AC → cAMP → PKA cascade. In contrast the 5HT1 receptor (e.g. on striatonigral and striatopallidal projection neurons: Emson et al., 2010) and 5-HT5 receptor (e.g. found in the GPe/I, STR, STN and SNc/SNr: Miguelez et al., 2014) are coupled to $G_{i/o}$ proteins, inhibiting this cascade. Finally, 5-HT2 receptors (e.g. on STN projection neurons: Emson et al., 2010) are positively coupled to phospholipase C (G_q) activating the IP3/DAG → Ca^{2+} → PKC cascade. Serotonin's effect on basal ganglia nuclei is thus complex, likely due to this heterogenous spread of different 5-HT receptor types and subtypes in different nuclei and cells, and interactions with other neurotransmitters. Here, we describe some ways in which serotonin might modulate basal ganglia activity.

In the striatum, serotonin exerts a tonic inhibitory influence over striatal activity, but it can also increase the firing rate of MSNs (for review see Miguelez et al., 2014) suggesting highly complex functions for striatal serotonin. For instance, striatal release induced by DRN stimulation can increase the firing frequency of MSNs (e.g. Park et al.,

1982), and stimulation of postsynaptic striatal 5-HT1A can increase locomotor activity (e.g. Mignon & William, 2002) through complex interactions with other neurotransmitter systems. In contrast, stimulation of 5-HT1A and 5-HT1B autoreceptors inhibits striatal serotonin release (e.g. Gerber et al., 1988; Knobelman et al., 2000), while postsynaptic activation of these receptors decreases corticostriatal glutamate release (e.g. 5-HT1A: Antonelli et al., 2005; Dupre et al., 2011, 2013) and increases striatal dopamine release (e.g. 5-HT1B, by inhibiting GABA release in the SNc: Gerber et al., 1988). The inhibitory effects of striatal serotonin seem to result from activation of 5-HT2 receptors (for review see Di Matteo et al., 2008). Both 5-HT2A and 5-HT2C agonists inhibit striatal MSN activity (e.g. El Mansari & Blier, 1997). This may be mediated through the inhibitory influence of striatal interneurons (e.g. serotonin strongly increases firing rates of cholinergic interneurons in vitro: Blomeley & Bracci, 2005). Here, serotonin binding to postsynaptic 5-HT2C receptors on cholinergic and fast-spiking interneurons, enhances both acetylcholine (Ach) and GABA release respectively (e.g. Blomeley & Bracci, 2009), which inhibits glutamatergic input to the striatum and inhibits spike-timing of MSNs respectively (Tepper & Koós, 2010). In sum, given that serotonin can both enhance and suppress striatal MSN activity, its role in regulating pathway activity is likely flexible, and sensitive to a number of different interactions between receptor types, cell types, and neurotransmitters within the striatum, as well as to different effects of serotonin in other brain regions. Below we describe some of those effects in the basal ganglia pathway nuclei.

In the GPe, serotonin increases firing frequency and maintains firing regularity (e.g. Chen et al., 2008). This is likely due to activation of 5-HT4 or 5-HT7 postsynaptic receptors, (e.g. Chen et al., 2008; Hashimoto and Kita, 2008) which could ultimately support and maintain GPe output and thus indirect pathway activity. However, 5-HT in the GPe could also serve an inhibitory function via binding at presynaptic 5-HT1B receptors which decreases presynaptic glutamate (from the STN) and GABA (from the STR) release in the GPe (Querejeta et al., 2005). This could result in reduced stimulation or inhibition, potentially decreasing or increasing GPe activity respectively. Less is known about the function of serotonin in the GPi (Miguelez et al., 2014).

Serotonin in the STN also has complex effects (e.g. 5-HT1A receptors decrease excitability, while 5-HT2C and 5-HT4 receptors increase excitability: e.g. Stanford et al., 2005; Xiang et al., 2005). In general serotonin limits STN firing frequency and burst activity (e.g. Liu et al., 2007; Aristieta et al., 2014), potentially decreasing indirect and hyperdirect pathway activity, and thence supporting behavioural activation. In the SNr, serotonin is mainly inhibitory by reducing burst-firing activity though presynaptic 5-HT1B receptors (e.g. Ding et al., 2013). This effect likely requires continuous availability of serotonin since its depletion can decrease SNr firing rate and in increase burst activity (Delaville et al., 2012). But serotonin can also increase SNr activity through selective stimulation of 5-HT2C receptors which excite SNr neurons, and 5-HT1B presynaptic receptors which inhibit GABA release from striatonigral neurons (e.g. Stanford & Lacey, 1996), essentially disinhibiting the SNr. Thus, while serotonin seems to keep SNr output 'in check', it may also cause it to 'ramp up' further inhibiting the thalamus and suppressing behaviour activation. In sum, while serotonin in the basal ganglia is mostly inhibitory, it can also be stimulatory, suggesting a complex regulatory function over basal ganglia activity.

Serotonin also modulates striatal dopamine function, where both stimulatory (e.g. serotonin infused directly into the striatum *in vivo,* enhances basal dopamine release: Benloucif & Galloway, 1991) and inhibitory (e.g. inhibition of dopamine synthesis and release observed *in vitro*: Nurse et al., 1988) effects have been found (for review see Navailles & De Deurwaerdère, 2011). However, serotonin receptors *do not* seem to be present on dopaminergic terminals within the striatum, but both SNc and VTA dopaminergic neurons (where 5-HT receptor mRNA is detected) may express at least some 5-HT receptors, suggesting that serotonin may regulate dopamine release indirectly. The mechanisms which control this process (e.g. which 5HT receptors are directly responsible for the stimulatory effects) are still not completely understood (Navailles & De Deurwaerdère, 2011). The functional significance of serotonergic regulation of dopamine transmission is also elusive (Miguelez et al., 2014). For example, removal of serotonergic input to SNc does not majorly alter SNc activity (e.g. Kelland et al., 1990) nor does selective serotonin reuptake inhibitor (SSRI)

administration (e.g. Prisco & Esposito, 1995). In sum, serotonin exerts some regulatory control over dopaminergic transmission, but the mechanisms, degree, and functions of this control are not yet understood.

4. Take Away Message

The current hypotheses for the neurobiological basis of environmentally induced stereotypic behaviours (the ‘Basal Ganglia [BG] Pathways’ and ’Cortico-Striatal-Thalamo-Cortical [CSTC] Circuits Hypotheses described in the main paper) are both largely based on an outdated understanding of how the cortico-basal ganglia system selects behaviours. As we have shown here, the underlying neurobiological mechanisms that control normal behaviour are very complex and currently are not fully understood. This updated view of cortico-basal ganglia anatomy and function has yet to be integrated into (or replace) our existing hypotheses on the neurobiology of stereotypic behaviours. However, it is clearly important. As we fail to find evidence supporting the existing, traditional hypotheses (reviewed in the main paper), it may well be necessary to consider these newly highlighted fundamental neuroscience findings in order to better understand how these mechanisms may be affected in stereotypic animals. This will require the refinement of old hypotheses, and the development of new hypotheses through more exploratory investigations into the functional anatomy of the cortico-basal ganglia system in stereotypic animals.

REFERENCES

Albin, R.L., Young, A.B., & Penney, J.B. (1989). The functional anatomy of basal ganglia disorders– Trends Neurosci. 12: 366–375.

Alcaraz, F., Fresno, V., Marchand, A.R., Kremer, E.J., Coutureau, E., & Wolff, M. (2018). Thalamocortical and corticothalamic pathways differentially contribute to goal-directed behaviors in the rat– Elife 7: 1–17.

Alexander, G.E., Delong, M.R., & Strick, P.L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex– Ann. Rev. Neurosci 9: 357–81.

Ambrosini, A., Bresciani, L., Fracchia, S., Brunello, N., & Racagni, G. (1995). Metabotropic glutamate receptors negatively coupled to adenylate cyclase inhibit N-methyl-D-aspartate receptor activity and prevent neurotoxicity in mesencephalic neurons in vitro– Mol. Pharmacol. 47: 1057–1064.

Antonelli, T., Fuxe, K., Tomasini, M.C., Bartoszyk, G.D., Seyfried, C.A., Tanganelli, S., & Ferraro, L. (2005). Effects of sarizotan on the corticostriatal glutamate pathways– Synapse 58: 193–199.

Aristieta, A., Morera-Herreras, T., Ruiz-Ortega, J.A., Miguelez, C., Vidaurrazaga, I., Arrue, A., Zumarraga, M., & Ugedo, L. (2014). Modulation of the subthalamic nucleus activity by serotonergic agents and fluoxetine administration– Psychopharmacology (Berl). 231: 1913–1925.

Aron, A.R. & Poldrack, R.A. (2006). Cortical and subcortical contributions to stop signal response inhibition: Role of the subthalamic nucleus– J. Neurosci. 26: 2424–2433.

Bamford, N.S., Zhang, H., Schmitz, Y., Wu, N.P., Cepeda, C., Levine, M.S., Schmauss, C., Zakharenko, S.S., Zablow, L., & Sulzer, D. (2004). Heterosynaptic dopamine neurotransmission selects sets of corticostriatal terminals– Neuron 42: 653–663.

Benloucif, S. & Galloway, M.P. (1991). Facilitation of dopamine release in vivo by serotonin agonists: studies with microdialysis– Eur. J. Pharmacol. 200: 1–8.

Bernal-Casas, D., Lee, H.J., Weitz, A.J., & Lee, J.H. (2017). Studying brain circuit function with dynamic causal modeling for optogenetic fMRI– Neuron 93: 522–532.

Bishop, G.A., Chang, H.T., & Kitai, S.T. (1982). Morphological and physiological properties of neostriatal neurons: An intracellular horseradish peroxidase study in the rat– Neuroscience 7: 179–189.

Blomeley, C. & Bracci, E. (2005). Excitatory effects of serotonin on rat striatal cholinergic interneurones– J. Physiol. 569: 715–721.

Blomeley, C.P. & Bracci, E. (2009). Serotonin excites fast-spiking interneurons in the striatum– Eur. J. Neurosci. 29: 1604–1614.

Borycz, J., Pereira, M.F., Melani, A., Rodrigues, R.J., Köfalvi, A., Panlilio, L., Pedata, F., Goldberg, S.R., Cunha, R.A., & Ferré, S. (2007). Differential glutamate-dependent and glutamate-independent adenosine A1 receptor-mediated modulation of dopamine release in different striatal compartments– J. Neurochem. 101: 355–363.

Calabresi, P., Picconi, B., Tozzi, A., Ghiglieri, V., & Di Filippo, M. (2014). Direct and indirect pathways of basal ganglia: A critical reappraisal– Nat. Neurosci. 17: 1022–1030.

Calabresi, P., Pisani, A., Mercuri, N.B., & Bernardi, G. (1996). The corticostriatal projection: From synaptic plasticity to dysfunctions of the basal ganglia– Trends Neurosci. 19: 19–24.

Calzavara, R., Mailly, P., & Haber, S.N. (2007). Relationship between the corticostriatal terminals from areas 9 and 46, and those from area 8A, dorsal and rostral premotor cortex and area 24c: An anatomical substrate for cognition to action– Eur. J. Neurosci. 26: 2005–2024.

Cazorla, M., Delmondes De Carvalho, F., Chohan, M.O., Shegda, M., Chuhma, N., Rayport, S., Ahmari, S.E., Moore, H., & Kellendonk, C. (2014). Dopamine D2 receptors regulate the anatomical and functional balance of basal ganglia circuitry– Neuron 81: 153–164.

Chang, H.T., Wilson, C.J., & Kitai, S.T. (1981). Single neostriatal efferent axons in the globus pallidus: A light and electron microscopic– Science (80-.). 213: 915–918.

Chen, L., Yung, K.K.L., Chan, Y.S., & Yung, W.H. (2008). 5-HT excites globus pallidus neurons by multiple receptor mechanisms– Neuroscience 151: 439–451.

Colwell, S.A. (1975). Thalamocortical-corticothalamic reciprocity: A combined anterograde-retrograde tracer technique– Brain Res. 92: 443–449.

Cowan, R.L. & Wilson, C.J. (1994). Spontaneous firing patterns and axonal projections of single corticostriatal neurons in the rat medial agranular cortex– J. Neurophysiol. 71: 17–32.

Crittenden, J.R., Graybiel, A.M., & Tepper, J.M. (2011). Basal ganglia disorders associated with imbalances in the striatal striosome and matrix compartments– Front. Neuroanat. 5: 59.

Cui, G., Jun, S.B., Jin, X., Pham, M.D., Vogel, S.S., Lovinger, D.M., & Costa, R.M. (2013). Concurrent activation of striatal direct and indirect pathways during action initiation– Nature 494: 238–242.

Delaville, C., Chetrit, J., Abdallah, K., Morin, S., Cardoit, L., De Deurwaerdère, P., & Benazzouz, A. (2012). Emerging dysfunctions consequent to combined monoaminergic depletions in Parkinsonism– Neurobiol. Dis. 45: 763–773.

Delong, M.R. (1990). Primate models of movement disorders of basal ganglia origin– Trends Neurosci. 13: 281–285.

Deschenes, M., Veinante, P., & Zhang, Z.-W. (1998). The organization of corticothalamic projections: Reciprocity versus parity– Brain Res. Rev. 28: 286–308.

Di Chiara, G. & Imperato, A. (1988). Opposite effects of mu and kappa opiate agonists on dopamine release in the nucleus accumbens and in the dorsal caudate of freely moving rats– J. Pharmacol. Exp. Ther. 244: 1067–1080.

Di Filippo, M., Calabresi, P., Filippo, M. Di, & Calabresi, P. (2010). Regulation of corticostriatal synaptic plasticity in physiological and pathological conditions– In: Handb. Basal Ganglia Struct. Funct. Elsevier Inc., Vol. 20, p. 219–229.

Di Matteo, V., Pierucci, M., Esposito, E., Crescimanno, G., Benigno, A., & Di Giovanni, G. (2008). Serotonin modulation of the basal ganglia circuitry: therapeutic implication for Parkinson's disease and other motor disorders– In: Prog. Brain Res. (Di Giovanni, G., Di Matteo, V., & Esposito, E., eds). Elsevier Science BV, Amsterdam, Vol. 172, p. 423–463.

Ding, S., Li, L., & Zhou, F.-M. (2013). Presynaptic serotonergic gating of the subthalamonigral glutamatergic projection– J. Neurosci. 33: 4875–4885.

Dupre, K.B., Ostock, C.Y., Eskow Jaunarajs, K.L., Button, T., Savage, L.M., Wolf, W., & Bishop, C. (2011). Local modulation of striatal glutamate efflux by serotonin 1A receptor stimulation in dyskinetic, hemiparkinsonian rats– Exp. Neurol. 229: 288–299.

Dupre, K.B., Ostock, C.Y., George, J.A., Eskow Jaunarajs, K.L., Hueston, C.M., & Bishop, C. (2013). Effects of 5-HT1A receptor stimulation on D1 receptor agonist-induced striatonigral activity and dyskinesia in hemiparkinsonian rats– ACS Chem. Neurosci. 4: 747–760.

Eblen, F. & Graybiel, A.M. (1995). Highly restricted origin of prefrontal cortical inputs to striosomes in the macaque monkey– J. Neurosci. 15: 5999–6013.

Eisinger, R.S., Cernera, S., Gittis, A., Gunduz, A., & Okun, M.S. (2019). A review of basal ganglia circuits and physiology: Application to deep brain stimulation– Park. Relat. Disord. 59: 9–20.

Eisinger, R.S., Urdaneta, M.E., Foote, K.D., Okun, M.S., & Gunduz, A. (2018). Non-motor characterization of the basal ganglia: Evidence from human and non-human primate electrophysiology– Front. Neurosci. 12: 385.

El Mansari, M. & Blier, P. (1997). In vivo electrophysiological characterization of 5-HT receptors in the guinea pig head of caudate nucleus and orbitofrontal cortex– Neuropharmacology 36: 577–588.

Emson, P.C., Waldvogel, H.J., & Faull, R.L.M. (2010). Neurotransmitter receptors in the basal ganglia– In: Handb. Basal Ganglia Struct. Funct. Elsevier Inc., Vol. 20, p. 75–96.

Feltz, P. & Albe-Fessard, D. (1972). A study of an ascending nigro-caudate pathway– Electroencephalogr. Clin. Neurophysiol. 33: 179–193.

Francois, C. (2004). Behavioural disorders induced by external globus pallidus dysfunction in primates II. Anatomical study– Brain 127: 2055–2070.

Freeze, B.S., Kravitz, A. V, Hammack, N., Berke, J.D., & Kreitzer, A.C. (2013). Control of basal ganglia output by direct and indirect pathway projection neurons– J. N 33: 18531–18539.

Fujiyama, F., Sohn, J., Nakano, T., Furuta, T., Nakamura, K.C., Matsuda, W., & Kaneko, T. (2011). Exclusive and common targets of neostriatofugal projections of rat striosome neurons: A single neuron-tracing study using a viral vector– Eur. J. Neurosci. 33: 668–677.

Gerber, R., Altar, C.A., & Liebman, J.M. (1988). Rotational behavior induced by 8-hydroxy-DPAT, a putative 5HT-1A agonist, in 6-hydroxydopamine-lesioned rats– Psychopharmacology (Berl). 94: 178–182.

Gerfen, C.R. (1984). The neostriatal mosaic: Compartmentalization of corticostriatal input and striatonigral output systems– Nature 311: 461–464.

Gerfen, C.R. (1989). The neostriatal mosaic: Striatal patch-matrix organization is related to cortical lamination– Science (80-.). 246: 385–388.

Gerfen, C.R. & Bolam, J.P. (2017). The neuroanatomical organization of the basal ganglia– In: Handb. Behav. Neurosci. Elsevier B.V., Vol. 24, p. 3–28.

Gerfen, C.R., Engber, T.M., Mahan, L.C., Susel, Z., Chase, T.N., Monsma, F.J., & Sibley, D.R. (1990). D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons– Science (80-.). 250: 1429–1432.

Gerfen, C.R. & Young, W.S. (1988). Distribution of striatonigral and striatopallidal peptidergic neurons in both patch and matrix compartments: An in situ hybridization histochemistry and fluorescent retrograde tracing study– Brain Res. 460: 161–167.

Gittis, A.H., Berke, J.D., Bevan, M.D., Chan, C.S., Mallet, N., Morrow, X.M., & Schmidt, R. (2014). New roles for the external globus pallidus in basal ganglia circuits and behavior– J. Neurosci. 34: 15178–15183.

Goldberg, J.A. & Wilson, C.J. (2010). The cholinergic interneurons of the striatum: Intrinsic properties underlie multiple discharge patterns– In: Handb. Basal Ganglia Struct. Funct. Elsevier Inc., Vol. 20, p. 133–149.

Gray, A.M., Rawls, S.M., Shippenberg, T.S., & McGinty, J.F. (1999). The κ-opioid agonist, U-69593, decreases acute amphetamine-evoked behaviors and calcium-dependent dialysate levels of dopamine and glutamate in the ventral striatum– J. Neurochem. 73: 1066–1074.

Graybiel, A.M. (1990). Neurotransmitters and neuromodulators in the basal ganglia– Trends Neurosci. 13: 244–254.

Graybiel, A.M. (2008). Habits, rituals, and the evaluative brain– Annu. Rev. Neurosci. 31: 359–387.

Groenewegen, H.J., Wouterlood, F.G., & Uylings, H.B.M. (2017). Organization of prefrontal-striatal connections– In: Handb. Behav. Neurosci. Elsevier B.V., Vol. 24, p. 423–438.

Groenewegen, H.J., Wright, C.I., Beijer, A.V.J., & Voorn, P. (1999). Convergence and segregation of ventral striatal inputs and outputs– Ann. N. Y. Acad. Sci. 877: 49–63.

Guo, Q., Wang, D., He, X., Feng, Q., Lin, R., Xu, F., Fu, L., & Luo, M. (2015). Whole-brain mapping of inputs to projection neurons and cholinergic interneurons in the dorsal striatum– PLoS One 10: p.e0123381.

Gurney, K., Prescott, T.J., & Redgrave, P. (2001a). A computational model of action selection in the basal ganglia: I. A new functional anatomy.– Biol. Cybern. 84: 401–410.

Gurney, K., Prescott, T.J., & Redgrave, P. (2001b). A computational model of action selection in the basal ganglia. II. Analysis and simulation of behaviour– Biol. Cybern. 84: 411–423.

Haber, S.N. (2003). The primate basal ganglia: Parallel and integrative networks– J. Chem. Neuroanat. 26: 317–330.

Haber, S.N. (2017). Integrative networks across basal ganglia circuits– In: Handb. Basal Ganglia Struct. Funct. Elsevier Inc., Vol. 24, p. 535–552.

Haber, S.N. & Calzavara, R. (2009). The cortico-basal ganglia integrative network: The role of the thalamus– Brain Res. Bull. 78: 69–74.

Haber, S.N., Fudge, J.L., & McFarland, N.R. (2000). Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum.– J. Neurosci. 20: 2369–82.

Haber, S.N., Kim, K.-S., Mailly, P., & Calzavara, R. (2006). Reward-related cortical inputs define a large striatal region in primates that interface with associative cortical connections, providing a substrate for incentive-based learning– J. Neurosci. 26: 8368–8376.

Hallett, P.J., Spoelgen, R., Hyman, B.T., Standaert, D.G., & Dunah, A.W. (2006). Dopamine D1 activation potentiates striatal NMDA receptors by tyrosine phosphorylation-dependent subunit trafficking– J. Neurosci. 26: 4690–4700.

Harvey, A.R. (1980). A physiological analysis of subcortical and commissural projections of areas 17 and 18 of the cat– J. Physiol. 302: 507–534.

Hashimoto, K. & Kita, H. (2008). Serotonin activates presynaptic and postsynaptic receptors in rat globus pallidus– J. Neurophysiol. 99: 1723–1732.

Hélie, S., Ell, S.W., & Ashby, F.G. (2015). Learning robust cortico-cortical associations with the basal ganglia: An integrative review– Cortex 64: 123–135.

Herkenham, M. & Pert, C.B. (1981). Mosaic distribution of opiate receptors, parafascicular projections and acetylcholinesterase in rat striatum– Nature 291: 415–418.

Hersch, S.M. & White, E.L. (1981). Thalamocortical synapses with corticothalamic projection neurons in mouse SmI cortex: Electron microscopic demonstration of a monosynaptic feedback loop– Neurosci. Lett. 24: 207–210.

Hillion, J., Canals, M., Torvinen, M., Casado, V., Scott, R., Terasmaa, A., Hansson, A., Atson, S., Olah, M.E., Mallol, J., Canela, E.I., Zoli, M., Agnatti, L.F., Ibanez, C.F., Lluis, C., Franco, R., Ferre, S., & Fuxe, K. (2002). Coaggregation, cointernalization, and codesensitization of adenosine A2a receptors and dopamine D2 receptors– J. Bioogical Chem. 277: 18091–18097.

Hintiryan, H., Foster, N.N., Bowman, I., Bay, M., Song, M.Y., Gou, L., Yamashita, S., Bienkowski, M.S., Zingg, B., Zhu, M., Yang, X.W., Shih, J.C., Toga, A.W., & Dong, H.W. (2016). The mouse cortico-striatal projectome– Nat. Neurosci. 19: 1100–1114.

Hunnicutt, B.J., Jongbloets, B.C., Birdsong, W.T., Gertz, K.J., Zhong, H., & Mao, T. (2016). A comprehensive excitatory input map of the striatum reveals novel functional organization– Elife 5: e19103.

Jimenez-Castellanos, J. & Graybiel, A.M. (1987). Subdivisions of the dopamine-containing A8-A9-A10 complex identified by their differential mesostriatal innervation of striosomes and extrastriosomal matrix– Neuroscience 23: 223–242.

Johnston, J.G., Gerfen, C.R., Haber, S.N., & van der Kooy, D. (1990). Mechanisms of striatal pattern formation: Conservation of mammalian compartmentalization– Dev. Brain Res. 57: 93–102.

Kalivas, P.W. & Stewart, J. (1991). Dopamine transmission in the initiation and expression of drug-and stress-induced sensitization of motor activity– Brain Res. Rev. 16: 223–244.

Karachi, C., Yelnik, J., Tandé, D., Tremblay, L., Hirsch, E.C., & François, C. (2005). The pallidosubthalamic projection: An anatomical substrate for nonmotor functions of the subthalamic nucleus in primates– Mov. Disord. 20: 172–180.

Kawaguchi, Y., Wilson, C.J., & Emson, P.C. (1990). Projection subtypes of rat neostriatal matrix cells revealed by intracellular injection of biocytin– J. Neurosci. 70: 3421–3439.

Keefe, K.A. & Horner, K.A. (2010). Neurotransmitter regulation of basal ganglia gene expression– In: Handb. Basal Ganglia Struct. Funct. Elsevier Inc., Vol. 20, p. 461–490.

Kelland, M.D., Freeman, A.S., & Chiodo, L.A. (1990). Serotonergic afferent regulation of the basic physiology and pharmacological responsiveness of nigrostriatal dopamine neurons– J. Pharmacol. Exp. Ther. 253: 803–811.

Kerr, J.N.D. & Plenz, D. (2002). Dendritic calcium encodes striatal neuron output during up-states– J. Neurosci. 22: 1499–1512.

Kincaid, A.E. & Wilson, C.J. (1996). Corticostriatal innervation of the patch and matrix in the rat neostriatum– J. Comp. Neurol. 374: 578–592.

Kita, H. & Jaeger, D. (2017). Organization of the globus pallidus– In: Handb. Behav. Neurosci. Elsevier Inc., Vol. 24, p. 259–276.

Kita, H. & Kitai, S.T. (1987). Efferent projections of the subthalamic nucleus in the rat: Light and electron microscopic analysis with the PHA-L method– J. Comp. Neurol. 260: 435–452.

Kita, T. & Kita, H. (2012). The subthalamic nucleus is one of multiple innervation sites for long-range corticofugal axons: A single-axon tracing study in the rat– J. Neurosci. 32: 5990–5999.

Knobelman, D.A., Kung, H.F., & Lucki, I. (2000). Regulation of extracellular concentrations of 5-hydroxytryptamine (5-HT) in mouse striatum by 5-HT(1A) and 5-HT(1B) receptors– J. Pharmacol. Exp. Ther. 292: 1111–1117.

Kravitz, A. V, Freeze, B.S., Parker, P.R.L., Kay, K., Thwin, M.T., Deisseroth, K., & Kreitzer, A.C. (2010). Regulation of Parkinsonian motor behaviors by optogenetic control of basal ganglia circuitry– Nature 466: 622–626.

Kravitz, A. V, Tye, L.D., & Kreitzer, A.C. (2012). Distinct roles for direct and indirect pathway striatal neurons in reinforcement– Nat. Neurosci. 15: 816–819.

Kress, G.J., Yamawaki, N., Wokosin, D.L., Wickersham, I.R., Shepherd, G.M.G., & Surmeier, D.J. (2013). Convergent cortical innervation of striatal projection neurons– Nat. Neurosci. 16: 665–667.

Künzle, H. (1975). Bilateral projections from precentral motor cortex to the putamen and other parts of the basal ganglia. An autoradiographic study in Macaca fascicularis– Brain Res. 88: 195–209.

Kupchik, Y.M., Brown, R.M., Heinsbroek, J.A., Lobo, M.K., Schwartz, D.J., & Kalivas, P.W. (2015). Coding the direct/indirect pathways by D1 and D2 receptors is not valid for accumbens projections– Nat. Neurosci. 18: 1230–1232.

Le Merrer, J., Becker, J.A.J., Befort, K., & Kieffer, B.L. (2009). Reward processing by the opioid system in the brain– Physiol. Rev. 89: 1379–1412.

Lee, E., Rhim, I., Lee, J.W., Ghim, J.-W., Lee, S., Kim, E., & Jung, M.W. (2016). Enhanced neuronal activity in the medial prefrontal cortex during social approach behavior– J. Neurosci. 36: 6926–6936.

Lei, W., Jiao, Y., Mar, N. Del, & Reiner, A. (2004). Evidence for differential cortical input to direct pathway versus indirect pathway striatal projection neurons in rats– J. Neurosci. 24: 8289–8299.

Liu, J., Chu, Y.X., Zhang, Q.J., Wang, S., Feng, J., & Li, Q. (2007). 5,7-dihydroxytryptamine lesion of the dorsal raphe nucleus alters neuronal activity of the subthalamic nucleus in normal and 6-hydroxydopamine-lesioned rats– Brain Res. 1149: 216–222.

Macpherson, T. & Hikida, T. (2019). Role of basal ganglia neurocircuitry in the pathology of psychiatric disorders– Psychiatry Clin. Neurosci. 73: 289–301.

Mailly, P., Aliane, V., Groenewegen, H.J., Haber, S.N., & Deniau, J.-M. (2013). The rat prefrontostriatal system analyzed in 3D: Evidence for multiple interacting functional units– J. Neurosci. 33: 5718–5727.

Mallet, N., Micklem, B.R., Henny, P., Brown, M.T., Williams, C., Bolam, J.P., Nakamura, K.C., & Magill, P.J. (2012). Dichotomous organization of the external globus pallidus– Neuron 74: 1075–1086.

Maneuf, Y.P., Mitchell, I.J., Crossman, A.R., & Brotchie, J.M. (1994). On the role of enkephalin cotransmission in the GABAergic striatal efferents to the globus pallidus– Exp. Neurol. 125: 65–71.

Martin, lee J. & Blackstone, C.D. (1992). Cellular Localization of a Metabotropic Glutamate Receptor in Rat Brain– Neuron 9: 259–270.

McFarland, N.R. & Haber, S.N. (2002). Thalamic relay nuclei of the basal ganglia form both reciprocal and nonreciprocal cortical connections, linking multiple frontal cortical areas– J. Neurosci. 22: 8117–8132.

Meredith, G.E., Ae, B.A.B., Ae, M.E.A., & Kelley, A.E. (2008). The structural basis for mapping behavior onto the ventral striatum and its subdivisions– Brain Struct. Funct. 213: 17–27.

Mignon, L. & William, W. (2002). Postsynaptic 5-HT1A receptors mediate an increase in locomotor activity in the monoamine-depleted rat– Psychopharmacology (Berl). 163: 85–94.

Miguelez, C., Morera-Herreras, T., Torrecilla, M., Ruiz-Ortega, J.A., & Ugedo, L. (2014). Interaction between the 5-HT system and the basal ganglia: Functional implication and therapeutic perspective in Parkinson's disease– Front. Neural Circuits 8: 1–9.

Mink, J.W. (1996). The basal ganglia: Focused selection and inhibition of competing motor programs– Pergamorr Prog. Neurobiol. 50: 381–425.

Mink, J.W. (2003). The basal ganglia and involuntary movements– Arch. Neurol. 60: 1365–1368.

Morelli, M., Simola, N., Popoli, P., & Carta, A.R. (2010). Role of adenosine in the basal ganglia– In: Handb. Basal Ganglia Struct. Funct. Elsevier Inc., Vol. 20, p. 201–217.

Mulder, A.H., Wardeh, G., Hogenboom, F., & Frankhnyzen, A.L. (1984). Kappa- and delta-opioid receptor agonists differentially inhibit striatal dopamine and acetylcholine release– Nature 60: 278–280.

Nambu, A., Tokuno, H., Hamada, I., Kita, H., Imanishi, M., Akazawa, T., Ikeuchi, Y., Hasegawa, N., & Hasegawa Excitatory, N. (2000). Excitatory cortical inputs to pallidal neurons via the subthalamic nucleus in the monkey– J. Neurophysiol. 84: 289–300.

Nambu, A., Tokuno, H., & Takada, M. (2002). Functional significance of the cortico-subthalamo-pallidal “hyperdirect” pathway– Neurosci. Res. 43: 111–117.

Navailles, S. & De Deurwaerdère, P. (2011). Presynaptic control of serotonin on striatal dopamine function– Psychopharmacology (Berl). 213: 213–242.

Nelson, A.B. & Kreitzer, A.C. (2014). Reassessing models of basal ganglia function and dysfunction– Annu. Rev. Neurosci. 37: 117–135.

Nurse, B., Russell, V.A., & Taljaard, J.J.F. (1988). Characterization of the effects of serotonin on the release of [3H]dopamine from rat nucleus accumbens and striatal slices– Neurochem. Res. 13: 403–407.

O’Donnell, P. (2010). Gating of limbic input to the ventral striatum– In: Handb. Basal Ganglia Struct. Funct. Elsevier Inc., Vol. 20, p. 367–379.

Oldenburg, I.A. & Sabatini, B.L. (2015). Antagonistic but not symmetric regulation of primary motor cortex by basal ganglia direct and indirect pathways– Neuron 86: 1174–1181.

Oorschot, D.E. (2010). Cell types in the different nuclei of the basal ganglia– In: Handb. Basal Ganglia Struct. Funct. Elsevier Inc., Vol. 20, p. 63–74.

Pan, W.X., Mao, T., & Dudman, J.T. (2010). Inputs to the dorsal striatum of the mouse reflect the parallel circuit architecture of the forebrain– Front. Neuroanat. 4: 147.

Parent, A. & Hazrati, L.-N. (1995). Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop– Brain Res. Rev. 20: 91–127.

Park, M.R., Gonzales-Vegas, J.A., & Kitai, S.T. (1982). Serotonergic excitation from dorsal raphe stimulation recorded intracellularly from rat caudate-putamen– Brain Res. 243: 49–58.

Pawlak, V. & Kerr, J.N.D. (2008). Dopamine receptor activation is required for corticostriatal spike-timing-dependent plasticity– J. Neurosci. 28: 2435–2446.

Plenz, D. (2003). When inhibition goes incognito: Feedback interaction between spiny projection neurons in striatal function– Trends Neurosci. 26: 436–443.

Plenz, D. & Wickens, J.R. (2010). The striatal skeleton– In: Handb. Basal Ganglia Struct. Funct. Elsevier Inc., Vol. 20, p. 99–112.

Plenz, D. & Wickens, J.R. (2017). The striatal skeleton: Medium spiny projection neurons and their lateral connections– In: Handb. Behav. Neurosci. Elsevier Inc., p. 99–112.

Pomata, P.E., Belluscio, M.A., Riquelme, L.A., & Murer, M.G. (2008). NMDA receptor gating of information flow through the striatum in vivo– J. Neurosci. 28: 13384–13387.

Prisco, S. & Esposito, E. (1995). Differential effects of acute and chronic fluoxetine administration on the spontaneous activity of dopaminergic neurones in the ventral tegmental area– Br. J. Pharmacol. 116: 1923–1931.

Querejeta, E., Oviedo-Chávez, A., Araujo-Alvarez, J.M., Quiñones-Cárdenas, A.R., & Delgado, A. (2005). In vivo effects of local activation and blockade of 5- HT1B receptors on globus pallidus neuronal spiking– Brain Res. 1043: 186–194.

Ramanathan, S., Hanley, J.J., Deniau, J.M., & Bolam, J.P. (2002). Synaptic convergence of motor and somatosensory cortical afferents onto GABAergic interneurons in the rat striatum– J. Neurosci. 22: 8158–8169.

Rawls, S.M. & McGinty, J.F. (2000). Delta opioid receptors regulate calcium-dependent, amphetamine-evoked glutamate levels in the rat striatum: An in vivo microdialysis study– Brain Res. 861: 296–304.

Redgrave, P., Coizet, V., & Reynolds, J. (2010). Phasic dopamine signaling and basal ganglia function– In: Handb. Basal Ganglia Struct. Funct. Elsevier Inc., Vol. 20, p. 549–559.

Redgrave, P. & Gurney, K. (2006). The short-latency dopamine signal: A role in discovering novel actions?– Nat. Rev. Neurosci. 7: 967–975.

Redgrave, P., Prescott, T.J., & Gurney, K. (1999). The basal ganglia: A vertebrate solution to the selection problem?– Neuroscience 89: 1009–1023.

Reid, M., Herrera-Marschitz, M., Hökfelt, T., Terenius, L., & Ungerstedt, U. (1988). Differential modulation of striatal dopamine release by intranigral injection of γ-aminobutyric acid (GABA), dynorphin A and substance P– Eur. J. Pharmacol. 147: 411–420.

Reiner, A. (2010a). The conservative evolution of the vertebrate basal ganglia– In: Handb. Basal Ganglia Struct. Funct. Elsevier Inc., Vol. 20, p. 29–62.

Reiner, A. (2010b). Organization of corticostriatal projection neuron types– In: Handb. Basal Ganglia Struct. Funct. Elsevier Inc., Vol. 20, p. 323–339.

Rock, C., Zurita, H., Wilson, C., & Apicella, A.J. (2016). An inhibitory corticostriatal pathway– Elife 5: 1–17.

Rouiller, E.M. & Welker, E. (2001). A comparative analysis of the morphology of corticothalamic projections in mammals– Brain Res. Bull. 53: 727–741.

Schad, C.A., Justice, J.B., & Holtzman, S.G. (1996). Differential effects of δ- and μ-opioid receptor antagonists on the amphetamine-induced increase in extracellular dopamine in striatum and nucleus accumbens– J. Neurochem. 67: 2292–2299.

Schiffmann, S.N., Jacobs, O., & Vanderhaeghen, J.-J. (1991). Striatal restricted adenosine A2 receptor (RDC8) is expressed by enkephalin but not by substance P neurons: An in situ hybridization histochemistry study– J. Neurochem. 57: 1062–1067.

Schmitt, L.I., Wimmer, R.D., Nakajima, M., Happ, M., Mofakham, S., & Halassa, M.M. (2017). Thalamic amplification of cortical connectivity sustains attentional control– Nature 545: 219–223.

Schulte, G. & Fredholm, B.B. (2003). Signalling from adenosine receptors to mitogen-activated protein kinases– Cell. Signal. 15: 813–827.

Schultz, W. (1998). Predictive reward signal of dopamine neurons– J. Neurophysiol. 80: 1–27.

Shen, W., Flajolet, M., Greengard, P., & Surmeier, D.J. (2008). Dichotomous dopaminergic control of striatal synaptic plasticity– Science (80-.). 321: 848–851.

Sherman, S.M. (2016). Thalamus plays a central role in ongoing cortical functioning– Nat. Neurosci. 19: 533–541.

Shigemoto, R., Kinoshita, A., Wada, E., Nomura, S., Ohishi, H., Takada, M., Flor, P.J., Neki, A., Abe, T., Nakanishi, S., & Mizuno, N. (1997). Differential presynaptic localization of metabotropic glutamate receptor subtypes in the rat hippocampus– J. Neurosci. 17: 7503–7522.

Shigemoto, R., Nomura, S., Ohishi, H., Sugihara, H., Nakanishi, S., & Mizuno, N. (1993). Immunohistochemical localization of a metabotropic glutamate receptor, mGluR5, in the rat brain– Neurosci. Lett. 163: 53–57.

Simonyan, K. (2019). Recent advances in understanding the role of the basal ganglia– F1000Research 8: Rev-122.

Sjöström, P.J. & Nelson, S.B. (2002). Spike timing, calcium signals and synaptic plasticity– Curr. Opin. Neurobiol. 12: 305–314.

Skeberdis, V.A., Lan, J.Y., Opitz, T., Zheng, X., Bennett, M.V.L., & Suzanne Zukin, R. (2001). mGluR1-mediated potentiation of NMDA receptors involves a rise in intracellular calcium and activation of protein kinase C– Neuropharmacology 40: 856–865.

Smith, I.D. & Grace, A.A. (1992). role of the subthalamic nucleus in the regulation of nigral dopamine neuron activity– SYNAPSE 12: 287–303.

Snyder, G.L., Allen, P.B., Fienberg, A.A., Valle, C.G., Huganir, R.L., Nairn, A.C., & Greengard, P. (2000). Regulation of phosphorylation of the GluR1 AMPA receptor in the neostriatum by dopamine and psychostimulants in vivo– J. Neurosci. 20: 4480–4488.

Stanford, I. & Lacey, M.G. (1996). Differential actions of serotonin, mediated by 5-HT1B and 5-HT2C receptors, on GABA-mediated synaptic input to rat substantia nigra pars reticulata neurons in vitro– J. Neurosci. 16: 7566–7573.

Stanford, I.M., Kantaria, M.A., Chahal, H.S., Loucif, K.C., & Wilson, C.L. (2005). 5-Hydroxytryptamine induced excitation and inhibition in the subthalamic nucleus: action at 5-HT(2C), 5-HT(4) and 5-HT(1A) receptors– Neuropharmacology 49: 1228–1234.

Steiner, H. (2010). Psychostimulant-induced gene regulation in corticostriatal circuits– In: Handb. Basal Ganglia Struct. Funct. Elsevier Inc., Vol. 20, p. 501–525.

Steiner, H. & Gerfen, C.R. (1996). Dynorphin regulates D1 dopamine receptor-mediated responses in the striatum: Relative contributions of pre- and postsynaptic mechanisms in dorsal and ventral striatum demonstrated by altered immediate-early gene induction– J. Comp. Neurol. 376: 530–541.

Steiner, H. & Gerfen, C.R. (1998). Role of dynorphin and enkephalin in the regulation of striatal output pathways and behavior– Exp Brain Res 123: 60–76.

Steiner, H. & Gerfen, C.R. (1999). Enkephalin regulates acute D2 dopamine receptor antagonist-induced immediate-early gene expression in striatal neurons– Neuroscience 88: 795–810.

Strick, P.L., Dum, R.P., & Mushiake, H. (1995). Basal ganglia “Loops” within the cerebral cortex– In: Funct. Cortico-Basal Ganglia Loop (Kimura, M. & Graybiel, A.M., eds). Springer-Verlag, New York, p. 106–124.

Surmeier, D.J., Day, M., Gertler, T., Chan, S., & Shen, W. (2010). D1 and D2 dopamine receptor modulation of glutamatergic signaling in striatal medium spiny neurons– In: Handb. Basal Ganglia Struct. Funct. Elsevier Inc., 6, Vol. 20, p. 113–132.

Surmeier, D.J., Song, W.J., & Yan, Z. (1996). Coordinated expression of dopamine receptors in neostriatal medium spiny neurons– J. Neurosci. 16: 6579–6591.

Tepper, J.M. & Koós, T. (2010). GABAergic interneurons of the striatum– In: Handb. Basal Ganglia Struct. Funct. Elsevier Inc., Vol. 20, p. 157–178.

Terman, D., Rubin, J.E., Yew, A.C., & Wilson, C.J. (2002). Activity patterns in a model for the subthalamopallidal network of the basal ganglia– J. Neurosci. 22: 2963–2976.

Ullmann, J.F.P., Watson, C., Janke, A.L., Kurniawan, N.D., Paxinos, G., & Reutens, D.C. (2014). An MRI atlas of the mouse basal ganglia– Brain Struct. Funct. 219: 1343–1353.

Vincent, S., Hökfelt, T., Christensson, I., & Terenius, L. (1982). Immunohistochemical evidence for a dynorphin immunoreactive striato-nigral pathway– Eur. J. Pharmacol. 85: 251–252.

Voorn, P., Van De Witte, S., Tjon, G., & Jonker, A.J. (1999). Expression of enkephalin in pallido-striatal neurons– Ann. N. Y. Acad. Sci. 877: 671–675.

Voorn, P., Vanderschuren, L.J.M.J., Groenewegen, H.J., Robbins, T.W., & Pennartz, C.M. (2004). Putting a spin on the dorsal-ventral divide of the striatum– Trend Neurosci. 27: 468–474.

Walker, R.H., Arbuthnott, G.W., Baughman, R.W., & Graybiel, A.M. (1993). Dendritic domains of medium spiny neurons in the primate striatum: Relationships to striosomal borders– J. Comp. Neurol. 337: 614–628.

Wall, N.R., De, M., Parra, L., Callaway, E.M., & Kreitzer, A.C. (2013). Differential innervation of direct-and indirect-pathway striatal projection neurons– Neuron 79: 347–360.

Walters, J.R. & Bergstrom, D.A. (2010). Synchronous activity in basal ganglia circuits– In: Handb. Basal Ganglia Struct. Funct. Elsevier Inc., Vol. 20, p. 429–443.

White, E.L. & Deamicis, R.A. (1977). Afferent and efferent projections of the region in mouse Sml cortex which contains the posteromedial barrel subfield– J. Comp. Neurol. 175: 455–481.

White, E.L. & Hersch, S.M. (1982). A quantitative study of thalamocortical and other synapses involving the apical dendrites of corticothalamic projection cells in mouse SmI cortex– J. Neurocytol. 11: 137–157.

Wickens, J.R. & Arbuthnott, G.W. (2010). Gating of cortical input to the striatum– In: Handb. Basal Ganglia Struct. Funct. Elsevier Inc., Vol. 20, p. 341–351.

Wickens, J.R. & Wilson, C.J. (1998). Regulation of action-potential firing in spiny neurons of the rat neostriatum in vivo– J. Neurophysiol. 79: 2358–2364.

Wilson, C.J. (1995). The contribution of cortical neurons to the firing pattern of striatal spiny neurons– In: Model. Inf. Process. Basal Ganglia (Houk, J.C., David, J.L., & Beiser, D.G., eds). MIT Press, Cambridge, p. 29–50.

Wilson, C.J. (2000). Striatal circuitry: Categorically selective, or selectively categorical?– In: Brain Dyn. striatal complex (Miller, R. & Wickens, J., eds). Hardwood Academic Publishers, Amsterdam, 1st ed., p. 289–305.

Wilson, C.J. (2017). The history of the basal ganglia: Cells and circuits– In: Handb. Behav. Neurosci. Elsevier Inc., Vol. 24, p. 45–62.

Wilson, C.J. & Groves, P.M. (1980). Fine structure and synaptic connections of the common spiny neuron of the rat neostriatum: A study employing intracellular injection of horseradish peroxidase– J. Comp. Neurol. 194: 599–615.

Wilson, C.J. & Kawaguchi, Y. (1996). The origins of two-state spontaneous membrane potential fluctuations of neostriatal spiny neurons– J. Neurosci. 16: 2397–2410.

Winter, C., Flash, S., Klavir, O., Klein, J., Sohr, R., & Joel, D. (2008). The role of the subthalamic nucleus in ‘compulsive’ behavior in rats– Eur. J. Neurosci. 27: 1902–1911.

Xiang, Z., Wang, L., & Kitai, S.T. (2005). Modulation of spontaneous firing in rat subthalamic neurons by 5-HT receptor subtypes– J. Neurophysiol. 93: 1145–1157.

Yin, H.H. & Lovinger, D.M. (2006). Frequency-specific and D2 receptor-mediated inhibition of glutamate release by retrograde endocannabinoid signaling– Proc. Natl. Acad. Sci. U. S. A. 103: 8251–8256.

Zahm, D.S. & Brog, J.S. (1992). On the significance of subterritories in the “accumbens” part of the rat ventral striatum– Neuroscience 50: 751–767.

Zhou, F.-W., Jin, Y., Matta, S.G., Xu, M., & Zhou, F.-M. (2009). An ultra-short dopamine pathway regulates basal ganglia output– J. Neurosci. 29: 1042–10435.