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COMPARTMENTAL FUNCTION AND MODULATION OF THE STRIATUM

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Abstract

The striatum plays a central role in guiding numerous complex behaviors, ranging from motor control to action selection and reward learning. The diverse responsibilities of the striatum are reflected by the complexity of its organization. In this review we will summarize what is currently known about the compartmental layout of the striatum, an organizational principle that is crucial for allowing the striatum to guide such a diverse array of behaviors. We will focus on the anatomical and functional properties of striosome (patch) and matrix compartments of the striatum, and how the engagement of these compartments is uniquely controlled by their afferents, intrinsic properties and neuromodulation. We will give examples of how advances in technology have opened the door to functionally dissecting the striatum's compartmental design, and close by offering thoughts on the future and relevance for human disease.

Keywords

Striosome; striatum; dopamine; Substance P; enkephalin; acetylcholine

The execution of precise movements and action-based sequences requires the convergence of inputs from cortical and subcortical structures onto the striatum, the primary input nucleus to the basal ganglia (Gerfen & Surmeier, 2011; Jin & Costa, 2015). These inputs target GABAergic spiny projection neurons (SPNs), the predominant striatal neuronal class, as well as a menagerie of interneurons, in a topographically organized manner (Assous & Tepper, 2019; Ebrahimi, Pochet, & Roger, 1992; Gerfen & Surmeier, 2011); coordinated engagement and interaction of these striatal neurons shapes SPN activity and thus striatal output and behavior (Amemori, Gibb, & Graybiel, 2011; Graybiel, 2008). SPNs account for 90–95% of all striatal neurons, and can be subdivided into at least two intermingled populations based on their axonal projection targets and expression of releasable peptides and dopamine receptors (Bolam, Hanley, Booth, & Bevan, 2000; Gerfen et al., 1990; Gerfen

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Conflict of Interest Statement

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& Wilson, 1996; Gerfen & Young, 1988; Kawaguchi, Wilson, & Emson, 1990; Le Moine, Normand, & Bloch, 1991; Onn, Berger, & Grace, 1994; Plotkin & Goldberg, 2018; Smith et al., 2016). In general, “direct pathway” SPNs (dSPNs) project directly to the output nuclei of the basal ganglia (though they also send axon “bridging” collaterals to the external globus pallidus (GPe) (Cazorla et al., 2014; Kawaguchi et al., 1990)) and express D1 dopamine receptors and substance P (SP); “indirect pathway” SPNs (iSPNs) project to the GPe (thus connecting to the basal ganglia output nuclei indirectly) and express D2 dopamine receptors and enkephalin (ENK) (Albin, Young, & Penney, 1989; Gerfen, 2006; Gong et al., 2003; Kravitz, Tye, & Kreitzer, 2012; Kreitzer, 2009; Wall, De La Parra, Callaway, & Kreitzer, 2013). This organization has several consequences that are central to basal ganglia function and control of movement and action selection: 1) dSPN activity promotes disinhibition of the thalamus and action initiation, while iSPN activity promotes the opposite and 2) fluctuations in striatal dopamine will have opposing effects on dSPNs and iSPNs (Albin et al., 1989; Alexander & Crutcher, 1990; Gerfen & Surmeier, 2011; Kravitz et al., 2012).

In addition to direct and indirect pathways, the striatum is organized into histochemically defined compartments, known as striosomes (or patches) and matrix (Gerfen, 1984, 1992a; Gerfen, Baimbridge, & Miller, 1985; Graybiel & Ragsdale, 1978; Herkenham, Edley, & Stuart, 1984; Jimenez-Castellanos & Graybiel, 1989; Pert, Kuhar, & Snyder, 1976). Both compartments contain dSPNs and iSPNs, but the compartmental activities of these SPNs have been associated with distinct behaviors. For example, while striosomes only occupy about 10–15% of the total striatal volume (Davis & Puhl, 2011; Desban, Kemel, Glowinski, & Gauchy, 1993; Johnston, Gerfen, Haber, & van der Kooy, 1990; Miyamoto, Katayama, Shigematsu, Nishi, & Fukuda, 2018; Morigaki & Goto, 2016), engagement of neurons within these compartments has been linked to the generation of drug-induced motor stereotypies, the selection of high-cost/high-value reward options and encoding expected outcomes during learning (Amemori et al., 2011; Bloem, Huda, Sur, & Graybiel, 2017; Canales & Graybiel, 2000; Friedman et al., 2015; Yoshizawa, Ito, & Doya, 2018).

How is compartment-specific activity of SPNs achieved in a behaviorally-relevant way? This likely involves an interplay between 1) selective activation of afferents, 2) modulation of neuronal activity and synaptic transmission by neuromodulators such as dopamine (DA), acetylcholine (ACh) and opioid peptides, and 3) interneuron mediated intra- and inter-compartmental signaling (Abudukeyoumu, Hernandez-Flores, Garcia-Munoz, & Arbuthnott, 2018; Brimblecombe & Cragg, 2017; Brimblecombe et al., 2018; Crittenden & Graybiel, 2011; Friedman et al., 2015). Despite evidence supporting the importance of compartment-specific striatal output in shaping behavior (Amemori et al., 2011; Bloem et al., 2017; Canales, 2005; Friedman et al., 2015), progress towards understanding the underlying mechanisms had largely been impeded by technical limitations. This is due to the low percentage of striosomal neurons and inability to visualize compartmental organization in live tissue. New tools allowing the visualization and manipulation of compartment-specific neurons have now given unprecedented functional access to this circuitry. While not an exhaustive review of the literature, the goal of this review is twofold. First, we will provide an update on the histochemical organization of the striatum and compartment-specific connectivity. Second, we will present examples of how newly available genetic and imaging

tools have shed light on the functional and modulatory mechanisms that shape compartment-specific activity.

Etiology of Striatal Compartmental Organization

Early studies examining acetylcholinesterase distribution in the striatum of adult humans, rhesus monkeys and cats revealed distinct compartments of low cholinesterase activity (Graybiel & Ragsdale, 1978). It soon became apparent that this histological pattern represented a coordinated organizational principle of the mature striatum, with neighboring neurons having more in common than just the local acetylcholinesterase activity level. For example, acetylcholinesterase-poor regions (striosomes/patches) also express high levels of the p-opioid receptor (MOR), while acetylcholinesterase-rich regions (matrix) express high levels of the Ca^{2+}-binding protein calbindin (Herkenham & Pert, 1981; Pert et al., 1976). Numerous other striatal proteins and genes are preferentially expressed in striosomes vs matrix-exhaustive lists are available elsewhere (Brimblecombe & Cragg, 2017; Crittenden & Graybiel, 2011). In general, the relative expression of dSPN-specific proteins is higher in striosomes and iSPN-specific proteins higher in matrix (Fujiyama et al., 2011; Guttenberg, Klop, Minami, Satoh, & Voorn, 1996; Levesque & Parent, 2005; Miyamoto et al., 2018). Supporting this observation, single cell tracing studies of striosome SPNs have reported higher percentages of neurons with axonal projections to basal ganglia output structures than to intermediate nuclei (Fujiyama et al., 2011; Levesque & Parent, 2005). This has led to an oft-cited dogma that striosomes are predominantly composed of dSPNs. This dogma, however, should be qualified. First, the matrix contains approximately equal numbers of dSPNs and iSPNs, so the contribution of the matrix to the direct pathway should not be sold short. Second, Miyamoto and colleagues recently demonstrated that striosomes can be classified into 5 types based on MOR, SP and ENK expression, suggesting that there may be heterogeneity in both striosome function and their primary pathway-associated targets (Miyamoto et al., 2018). Indeed, SP-rich striosomes (which are primarily found in the medial striatum in rodents) may contain up to 70% dSPNs, but the percentage of dSPNs is far lower (as low as 40%) in other striosome regions (Miyamoto et al., 2018).

The groundwork for the striatum's compartmental organization is laid embryonically. In fact, striosomes represent some of the oldest and earliest assembled circuit components in the striatum. Striatal cells migrate from the lateral ganglionic eminence in two distinct waves, beginning around embryonic days 9.5 to 13.5 in rodents (Kelly et al., 2018; Tinterri et al., 2018). The cells in the first wave ultimately correspond to striosomal SPNs and migrate to their destinations around the same time as the earliest cortical (layer 6) neurons do, putting them in position to receive early corticostriatal as well as early thalamostriatal inputs (Fishell & van der Kooy, 1987; Graybiel, 1984; Graybiel & Hickey, 1982; Hagimoto, Takami, Murakami, & Tanabe, 2017; Moon Edley & Herkenham, 1984; Nakamura, Hioki, Fujiyama, & Kaneko, 2005; Song & Harlan, 1994). Immature striosomes are also the recipients of the earliest dopaminergic inputs. Dopaminergic nigrostriatal fibers initially form "dopamine islands" within the striatum, before spreading to the more homogenous distribution seen in the adult (Olson, Seiger, & Fuxe, 1972; Tennyson et al., 1972). These dopamine islands overlap with immature striosome compartments (Davis & Puhl, 2011; Graybiel, Pickel, Joh, Reis, & Ragsdale, 1981; Hagimoto et al., 2017; Miura, Saino-Saito,

Masuda, Kobayashi, & Aosaki, 2007). Once positioned, striosome cells become mostly stationary and cluster together, whereas matrix cells continue to actively migrate in a multidirectional manner during late embryonic development (Hagimoto et al., 2017). The homogenous mix of dSPNs and iSPNs observed in adults is this result of a parallel, active intermixing of iSPNs (Tinterri et al., 2018). While striosomes form a continuous labyrinthine network that extends through the striatum (Graybiel & Ragsdale, 1978), it should be noted that recent work has discovered the presence of scattered SPNs within the matrix (termed “exo-patches”) that are more similar to striosome than matrix SPNs in terms of genetic profiles, birth date, synaptic connectivity and modulation by neuropeptides (Crittenden & Graybiel, 2011; Newman, Liu, & Graybiel, 2015; Smith et al., 2016). It should also be noted that the mature morphological appearance of compartmentalization varies by region, with striosomes in dorsal and central striatal regions having canonical “patchy” appearances, and those ventrally often appearing more like “swirls” (Brimblecombe & Cragg, 2017). The precise function and etiology of exo-patches and morphological differences in compartmentalization remain to be determined.

Compartment Specific Afferent and Efferent Pathways

A feature of striatal compartmental organization is the segregation of striatal inputs and outputs. Decades of research exploring the compartmental targets of striatal afferents uncovered several themes. First, though some overlap certainly exists, afferents are often categorically segregated: in the dorsal striatum limbic-associated cortical and subcortical regions (including portions of the prelimbic, orbitofrontal and anterior insular cortices and basolateral nuclei of the amygdala) preferentially innervate striosomes, whereas projections from somatosensory and motor cortices preferentially innervate the matrix. Second, just as not all striosomes are histochemically homogenous, compartment-specific innervation patterns vary across striatal regions (Canales, 2005; Donoghue & Herkenham, 1986; Eblen & Graybiel, 1995; Flaherty & Graybiel, 1994; Friedman et al., 2015; Gerfen, 1984, 1985, 1989; Graybiel & Ragsdale, 1978; Kincaid & Wilson, 1996; Levesque, Charara, Gagnon, Parent, & Deschenes, 1996; Ragsdale & Graybiel, 1988, 1990). Despite the wealth of evidence for compartmental segregation of striatal afferents, recent work employing new methodologies has called much of this into question (we refer the reader to Brimblecombe and Cragg (2017) and Gerfen et al. (2013) for further information about new mouse lines used to isolate and interrogate compartments and their afferents/efferents). Using bacterial artificial chromosome (BAC) mice that preferentially express cre recombinase in striosomes vs matrix neurons and cutting-edge viral tracing techniques, Smith and colleagues reported that afferents from most cortical regions showed minimal compartmental preference (Smith et al., 2016). They did find, however, that subcortical regions such as the septum, hypothalamus and bed nucleus of the stria terminalis preferentially project to the striosomes. The reason for these discrepancies is not clear, but likely relates to methodological differences. For example, the retroviral tracing techniques employed in the latter study are well suited to detect differences in the number of presynaptically connected neurons, but lack sensitivity in detecting differences in synapse number between connected neurons. Consistent with this, recent studies utilizing viral tracing techniques that functionally and visually label corticostriatal axonal fields detect preferential connectivity between the

prelimbic cortex and striosomes and anterior cingulate cortex and matrix (Friedman et al., 2017; Friedman et al., 2015).

Both compartments contain dSPNs and iSPNs that project to the substantia nigra pars reticulata (SNr) / internal globus pallidus (GPi; entopeduncular nucleus in mice) and GPe, respectively, and hence contribute to canonical direct and indirect pathways (Fujiyama et al., 2011). Due to the sheer numbers of matrix vs striosome SPNs, however, the source of GPe/SNr/GPi synaptic inhibition is likely biased towards SPNs residing in the matrix (Fujiyama et al., 2011; Gerfen & Young, 1988; Jimenez-Castellanos & Graybiel, 1989; Levesque & Parent, 2005; Rajakumar, Elisevich, & Flumerfelt, 1993; Tokuno, Chiken, Kametani, & Moriizumi, 2002). But striosomal dSPNs may also innervate other targets, endowing them with the capacity to influence unique aspects of behavior. Work in non-human primates has shown that striosome SPNs innervate ventral pallidum neurons and "border neurons" situated at the edge of the GPi, which then inhibit or excite neurons within the lateral habenula, respectively. This disynaptic circuit offers a mechanism by which striosomal output can feasibly guide negative reward prediction and motivational decision-making (Hong et al., 2019; Hong & Hikosaka, 2013). It was also discovered early on that in addition to targeting the output nuclei of the basal ganglia, many striosome dSPNs directly target dopaminergic neurons of the substantia nigra pars compacta (SNc) (Gerfen, 1985; Jimenez- Castellanos & Graybiel, 1987). While a recent study using cre-dependent viral tracing techniques to target SNc neurons suggests that a population of matrix and exo-patch SPNs may do the same (Smith et al., 2016), 1) the density of retrogradely labeled SPNs projecting to the SNc is higher in striosomes, and 2) viral labeling of BAC transgenic mice preferentially expressing cre recombinase in striosome vs matrix neurons has demonstrated differential outputs to the SNc (Gerfen, Paletzki, & Heintz, 2013; Smith et al., 2016). Furthermore, it is clear that axon terminals originating from striosome SPNs form tightly wound associations with the ventrally extending dopaminergic dendrites of SNc neurons. Termed "striosome-dendron bouquets", these associations have been proposed to represent computational units allowing striosomal regulation of dopaminergic neurons (Crittenden et al., 2016). Though the precise function of striosome-dendron bouquets is unknown, one possibility is that striosomal axons within the bouquets regulate local dopamine release from dendrites within the SNr. An alternate (and not mutually exclusive) possibility is that the bouquets serve as a homeostat, whereby elevations in striatal dopamine will alter the activity of striosomal neurons projecting to the SNc, leading to direct inhibition of dopaminergic neurons and thus reducing dopamine release in the striatum.

Inter-compartmental Communication

SPN dendrites and axon collaterals generally respect compartmental borders, resulting in minimal inter- compartmental synaptic communication (Bolam, Izzo, & Graybiel, 1988; Fujiyama et al., 2011; Kawaguchi, Wilson, & Emson, 1989; Lopez-Huerta et al., 2016; Penny, Wilson, & Kitai, 1988). Many local striatal interneurons, however, have dendrites and axons that freely traverse compartmental borders, positioning them to serve as a functional bridge between compartments. Indeed, though widely distributed (and often at higher densities in the matrix), cholinergic interneurons (CINs), parvalbumin-expressing fast-spiking interneurons, neuropeptide Y- expressing interneurons and calretinin- expressing

interneurons are frequently located along striosomal borders in what have been termed "peristriosomal boundaries", anatomically and functionally defined micro-regions that may potentially shepherd information flow between compartments (Bernacer, Prensa, & Gimenez-Amaya, 2012; Brimblecombe & Cragg, 2015, 2017; Cowan, Wilson, Emson, & Heizmann, 1990; Kubota & Kawaguchi, 1993; Matamales, Gotz, & Bertran-Gonzalez, 2016; Rushlow, Naus, & Flumerfelt, 1996). A great deal is known about how interneurons guide circuit function within compartments, or at least in the presumptive matrix (Assous & Tepper, 2019; Banghart, Neufeld, Wong, & Sabatini, 2015; Crittenden et al., 2017), and clues suggesting how local microcircuitry preferentially impacts striosome vs matrix SPN activity are emerging (Banghart et al., 2015; Friedman et al., 2015). But the precise role that interneurons play in functionally linking striosome and matrix circuits is a crucial area for future study (see (Amemori et al., 2011).

Functional Differences between Striosome and Matrix SPNs

Compartmental Differences in Intrinsic Excitability

Because 1) technical limitations typically impede the targeted interrogation of compartments in live striatal tissue and 2) there is a substantial volume disparity between striosomes and matrix, most published studies of striatal function likely reflect phenomena occurring in the matrix. The first study to systematically compare the electrophysiological properties of SPNs in striosomes vs matrix employed intracellular recordings followed by post-hoc histological identification in rat brain slices (Kawaguchi et al., 1989). While this heroic study reported overall similarities in membrane properties and firing characteristics, more recent studies employing patch clamp techniques in genetically-labeled mice have begun to uncover differences. One theme that has arisen is that SPNs in striosomes are intrinsically more excitable than their counterparts in the matrix. Using patch clamp recordings in immature (postnatal days 12–32) tyrosine hydroxylase (TH)-GFP transgenic mice (to visualize presumptive striosomes), Miura and colleagues found that striosome SPNs have a higher input resistance and are more depolarized than those in the matrix (Miura et al., 2007). Similarly, using patch clamp recordings and CaIDAG-GEFI-GFP transgenic mice to visualize matrix neurons, Crittenden and colleagues found that not only are striosome SPNs more depolarized than those in the matrix, but they require less current injection to fire action potentials and fire at a higher frequency in response to similar current injections compared to matrix SPNs (Crittenden et al., 2017).

What is less clear is how such differences relate to dSPNs and iSPNs within and between compartments. Within the presumptive matrix, numerous lines of evidence suggest that iSPNs are more excitable than dSPNs. This includes measures of intrinsic somatic and dendritic excitability, action potential threshold and frequency of spontaneous excitatory synaptic inputs (Cepeda et al., 2008; Day et al., 2006; Gertler, Chan, & Surmeier, 2008; Kreitzer & Malenka, 2007). Using adult double transgenic mice to identify striosomes (Sepw1NP67-Cre mice, virally infected with cre-dependent tdTomato) and dSPNs (D1-eGFP mice), Smith and colleagues showed that striosome dSPNs fire more spikes in response to suprathreshold current injection than matrix dSPNs (Smith et al., 2016). This is consistent with preliminary data collected in our lab from Nr4a1-eGFP x drd1-tdTomato

double transgenic mice (see our preprint: http://dx.doi.org/10.2139/ssrn.3263630). Interestingly, Smith and colleagues went on to show that this excitable phenotype extends to D1-receptor expressing exo-patch neurons as well (Smith et al., 2016). Whether or not iSPNs in striosomes are more excitable than iSPNs in the matrix, and if the same dSPN vs iSPN dichotomy observed in presumptively matrix recordings holds up within striosomes, remains to be determined.

Modulation of Synaptic Activity and Function in Striosome and Matrix Compartments

While differences in presynaptic inputs and postsynaptic excitability will shape compartment-specific activity and striatal output, it has become clear that neuromodulation also plays a major role. A growing number of studies (referenced below) have discovered that neuromodulation is not homogenous throughout the striatum, and can often be compartment-specific (Table 1). Such compartmental differences can be due to a variety of factors, some identified and some still mysterious, including differences in neuromodulator source, release and receptor expression. Below we will present key examples highlighting how differential neuromodulation may affect compartment-specific striatal circuit function and output.

Opioid Receptors—The striatum expresses three classes of opioid receptors: p (MORs), *d* (DORs) and κ (KORs). Unlike KORs (the endogenous ligand of which is dynorphin), which are expressed homogenously throughout the striatum, MORs and DORs are enriched in striosomes and exo-patch neurons (Graybiel, 1990; Koizumi et al., 2013; Miura et al., 2007; Smith et al., 2016). Despite the striosomal-expression pattern of MORs and DORs, their endogenous ligand, enkephalin, is positioned to modulate synaptic transmission throughout the striatum. Presynaptically expressed MORs inhibit glutamatergic excitatory synaptic transmission to SPNs similarly in both striosome and matrix compartments (Miura et al., 2007). While it was initially presumed that this MOR-mediated inhibition occurred at corticostriatal synapses (Blomeley & Bracci, 2011; Miura et al., 2007), more recent studies have shown that thalamostriatal inputs are the targets of MORs, while corticostriatal inputs are attenuated by DORs (Atwood, Kupferschmidt, & Lovinger, 2014; Birdsong et al., 2019). Though opioid receptor-mediated attenuation of excitatory inputs to SPNs may be similar across compartments, attenuation of inhibitory inputs is not. A pioneering study by Miura and colleagues demonstrated that pharmacological activation of presynaptic MORs selectively attenuates GABA release and resulting postsynaptic inhibitory currents within striosomes, but not matrix (Miura et al., 2007). This preferential action of opioid receptor activation on inhibitory inputs has since been extended to include exo-patches (Smith et al., 2016). What was not clear from these studies was the local microcircuitry that was engaged. This issue was tackled in an elegant study by Banghart and colleagues, who used genetic and optical techniques (prodynorphin-EGFP mice to visualize striosomes, crossed with pathway-specific cre lines to target channelrhodopsin to dSPNs or iSPNs) to dissect the circuits involved (Banghart et al., 2015). While both dSPNs and iSPNs within striosomes express MORs, striosomal iSPNs contain functional DORs. Activation of DORs within striosomes attenuates iSPN-mediated collateral inhibition of dSPNs, promoting the disinhibition of striosome-associated targets such as the SNc (Banghart et al., 2015). The involvement of DORs (rather than MORs) in this phenomenon is at odds with earlier reports, but may reflect

limitations in pharmacological tools (Banghart et al., 2015) or a developmental shift in receptor expression or function. It should be noted that disinhibition of striosomal output may also be achieved in opioid receptor-independent ways. For example, cannabinoid-1 receptors (CB1Rs), which attenuate presynaptic glutamate and GABA release in much the same way as opioid receptors do (Adermark, Talani, & Lovinger, 2009; Atwood et al., 2014), are preferentially expressed in SPN axon collaterals within striosomes in the dorsolateral striatum (Davis et al., 2018). As presynaptic CB1Rs are key determinants of endocannabinoid-mediated long term depression (LTD) within the striatum (Lovinger, 2010), it is tempting to speculate that the propensity for LTD at inhibitory SPN-SPN collateral connections or extrastriatal SPN axonal targets is augmented in striosomes.

Substance P—SP, which is released by dSPNs (Gerfen, 1992b), can also be used to distinguish striosomes and matrix as it is more highly expressed in the striosomes of adult rodents (Crittenden & Graybiel, 2011). SP is an endogenous ligand for neurokinin-1 (NK1) receptors, which are present on glutamatergic terminals within the striatum (Jakab & Goldman-Rakic, 1996) as well as several striatal interneuron populations (Chen, Cao, Liu, Ju, & Chan, 2003; Govindaiah, Wang, & Cox, 2010). Activity-dependent release of SP by SPN axon collaterals can potentiate responses to cortical inputs in neighboring SPNs, in a NK1 receptor-dependent manner (Blomeley, Kehoe, & Bracci, 2009). It remains to be determined if such facilitation is dominant in striosomes, as may be predicted by the expression profile of SP. NK1 receptor activation can also modulate dopamine release, though early descriptions in the striatum were inconsistent (Boix, Huston, & Schwarting, 1992; Starr, 1982; Tremblay, Kemel, Desban, Gauchy, & Glowinski, 1992). An elegant study by Brimblecombe and Cragg (2015) has recently shed light on this process, demonstrating that SP modulation of dopamine release in the striatum is not only compartment-specific but bidirectional (Brimblecombe & Cragg, 2015), a finding that likely explains the source of earlier confusion. Specifically, SP enhances striatal dopamine release in striosomes but not matrix. Moreover, the authors uncovered a border region between compartments ("peristriosomal boundaries") where SP *decreases* dopamine release (Brimblecombe & Cragg, 2015). This finding not only clarified the role of SP in striatal circuit function, but described an additional functional region of striatal circuitry within the striosome/matrix organization, the significance of which is only beginning to be understood (Brimblecombe & Cragg, 2017).

Acetylcholine—CINs are the main source of ACh in the striatum. While CIN cell bodies tend to reside in the matrix and peristriosomal boundaries, and their neuropil is more extensive in the matrix, CINs are indeed present in both compartments and their processes do cross striosome-matrix boundaries (Abudukeyoumu et al., 2018; Bernacer, Prensa, & Gimenez-Amaya, 2007; Brimblecombe & Cragg, 2017; Crittenden, Lacey, Lee, Bowden, & Graybiel, 2014; Crittenden et al., 2017; Goldberg & Reynolds, 2011; Graybiel, Baughman, & Eckenstein, 1986; Inoue, Suzuki, Nishimura, & Miura, 2016; Jakab & Goldman-Rakic, 1996). Cholinergic signaling modulates myriad aspects of striatal circuit function (including cellular excitability, synaptic transmission and plasticity, dopamine release and circuit responses to salient cues), which are reviewed elsewhere (Abudukeyoumu et al., 2018; Gerfen & Surmeier, 2011; Goldberg & Reynolds, 2011; Plotkin & Goldberg, 2018), but we

are only beginning to understand how this modulation occurs within the context of the striatum's compartmental organization.

Fundamental to understanding compartmental differences in cholinergic signaling is the recent observation that CIN activity itself may be differentially modulated in striosomes vs matrix. CINs excite several classes of striatal GABAergic interneurons, via postsynaptic nicotinic acetylcholine receptors (nAChRs), which in turn send GABAergic projections back to CINs, forming an inhibitory feedback loop (Abudukeyoumu et al., 2018; Assous & Tepper, 2019). This feedback loop is considerably stronger in the matrix (Inoue et al., 2016). What is responsible for this compartmental difference? It is likely that the mechanism is rooted in the archetypal expression pattern of acetylcholinesterase, which is high in the matrix and low in striosomes (Graybiel & Ragsdale, 1978). Given that CINs release ACh in both striosomes and matrix (Crittenden et al., 2017; Inoue et al., 2016), it is reasonable to speculate that the dearth of acetylcholinesterase may amplify the lifespan of synaptically released ACh. Indeed, the frequency of nAChR-mediated GABAergic inputs to CINs is attenuated by both pharmacological application of ACh or inhibition of acetylcholinesterase (Inoue et al., 2016), perhaps reflecting higher basal ACh tone and desensitization of nAChRs in striosomes.

In addition to sending axon collaterals back to CINs, several populations of striatal interneurons also send GABAergic projections to SPNs, allowing CINs to modulate SPN activity in a multisynaptic nAChR- and GABA receptor- dependent manner (Assous & Tepper, 2019; English et al., 2011; Faust, Assous, Tepper, & Koos, 2016; Luo, Janssen, Partridge, & Vicini, 2013; Nelson et al., 2014). Recent work suggests that a functional multisynaptic connection from CINs to SPNs is present in both compartments, and it may be stronger in striosomes (Crittenden et al., 2017). Specifically, using CalDAG-GEFI-EGFP mice to visualize matrix neurons Crittenden and colleagues demonstrated that optogenetic stimulation of CINs disrupt the firing patterns of SPNs in *ex vivo* striatal slices in a nAChR-dependent way, though the dependence upon GABA remains unclear. Furthermore, repeated *in vivo* administration of D-amphetamine, which induces behavioral stereotypies and preferential cFos induction in striosomes relative to reduced activation in matrix, abolishes the ability of CINs to disrupt SPN firing (Canales & Graybiel, 2000; Crittenden et al., 2017). This, along with observations that 1) destruction of striatal CINs (and somatostatinergic interneurons) prevents the above drug-induced striosome/matrix pattern of cFos induction, 2) pharmacological blockade of striatal cholinergic signaling increases drug-induced stereotypies and 3) globally elevating acetylcholine release also exacerbates drug-induced stereotypies (Aliane, Perez, Bohren, Deniau, & Kemel, 2011; Crittenden et al., 2014; Janickova, Prado, Prado, El Mestikawy, & Bernard, 2017; Saka, Iadarola, Fitzgerald, & Graybiel, 2002; see also the preprint by Crittenden et al., deposited in bioRxiv on July 22, 2019 https://www.biorxiv.org/content/10.1101/709246v1), suggests that a precise balance of striatal cholinergic signaling may be required to shape striosome-linked behaviors and prevent pathological stereotypy.

Dopamine—DA modulation of striatal circuit function plays an integral role in shaping behavioral output (Cox & Witten, 2019; Gerfen & Surmeier, 2011; Plotkin & Goldberg, 2018). Canonically, elevations in dopamine will promote activity of dSPNs and suppress

activity of iSPNs, ultimately favoring disinhibition of the thalamus (Albin et al., 1989; Alexander & Crutcher, 1990; Gerfen & Surmeier, 2011). Although all areas of the striatum receive dense dopaminergic innervation, the source of dopaminergic fibers varies by region and compartment. The dorsal tier of the SNc and the ventral tegmental area preferentially supply DA to dorsal and ventral striatal regions, respectively, with the primary targets being in the matrix. The primary source of DA inputs to striosomes, however, is the ventral tier of the SNc (Gerfen, Herkenham, & Thibault, 1987; Haber, 2014; Matsuda et al., 2009; Prensa & Parent, 2001). This heterogeneous innervation pattern, along with compartmental gradients of other neuromodulators that locally regulate DA release (Brimblecombe & Cragg, 2017), set a plausible framework for compartmentally-dissociated DA signaling. Indeed, the pioneering study by Canales and Graybiel (2000) mentioned above demonstrated that repeated activation of the dopaminergic system induces preferential immediate early gene expression in striosomes relative to decreased induction in the matrix (Canales & Graybiel, 2000).

As described above, SP modulation of striatal DA release is spatially heterogeneous and compartment-specific (Brimblecombe & Cragg, 2015). Recent work by Salinas and colleagues (2016) has demonstrated that evoked DA release, and its modulation by cocaine, is also compartment and region specific. Using acute striatal slices from Nr4a1-GFP mice to visualize striosomes (Davis & Puhl, 2011), the authors demonstrated that electrically evoked DA release is lower in striosomes than the surrounding matrix in the dorsal striatum, and this relationship is reversed in the ventral striatum (Salinas, Davis, Lovinger, & Mateo, 2016). Furthermore, cocaine augmentation of DA release is greater in striosomes than matrix in the dorsal striatum, an observation that can only be partially explained by differences in dopamine transporter inhibition. Importantly, although activation of presynaptic nAChRs promotes local DA release (Threlfell et al., 2012), this mechanism appears to be similar in striosomes and matrix and does not account for the observed differences in evoked release (Salinas et al., 2016). Why compartmental differences in acetylcholinesterase activity correlate with nAChR-mediated modulation of GABAergic signaling (Inoue et al., 2016) but not DA release (Salinas et al., 2016) is unclear, but may reflect differences in basal CIN activity and ACh levels achieved by the unique experimental slice conditions.

While the regulation of DA release is clearly different in striosomes and matrix, it remains to be determined if postsynaptic DA signaling is similar in SPNs of each compartment. Specifically, although dSPNs and iSPNs in striosomes and matrix express comparable DA receptors, the consequences of DA receptor activation are ultimately determined by additional factors, including the functional state of the neuron and the ion channels it possesses (Cepeda, Colwell, Itri, Chandler, & Levine, 1998; Gerfen & Surmeier, 2011; Liu et al., 2004). As described above, SPNs do exhibit compartment-specific physiological properties, raising the caveat that functional modulation by DA may differ as well. Indeed, preliminary data from our laboratory suggest that that this may be the case (https://dx.doi.org/10.2139/ssrn.3263630).

Summary and going forward

The complexity of striatal compartmentalization and its role in shaping behavior are only starting to become clear. While decades of research have led to an overall model of basal ganglia function where limbic and sensorimotor loops are compartmentalized to guide unique aspects of behavior, newly developed tools are opening the door to test fundamental hypotheses in functioning circuits and living animals. Of keen interest to public health will be using these tools to follow old clues about the pathologies underlying disease states. For example, the correlation between striosome activation and repetitive behaviors has overt implications for conditions such as obsessive-compulsive disorder (Canales & Graybiel, 2000) - can dissection of the mechanism underlying drug-induced engagement of striosomes shed light on the underlying cause of this disorder? Pathological reports and animal models suggest that SNc neurons projecting to striosomes vs matrix may be differentially vulnerable in Parkinson's disease (Gibb & Lees, 1991; Moratalla et al., 1992) - does this play a role in disease progression, and are there compartment-specific responses to DA replacement strategies that need to be identified and considered? One of the earliest pathologies in Huntington's disease is the loss or alteration of neurons within striosomes (Hedreen & Folstein, 1995; Menalled et al., 2002). Interestingly, choreic symptoms of Huntington's disease are associated with elevated dopamine, and dopamine blockers such as tetrabenazine are used to treat motor symptoms (Zuccato, Valenza, & Cattaneo, 2010). Might the pathological dopamine fluctuations seen in early stages of Huntington's disease be the result of dysfunctional striosomal inhibition of SNc neurons? As technology continues to advance, so too will our ability to address such questions.

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SIGNIFICANCE STATEMENT

The way in which striatal compartmental organization influences complex behavioral patterns remains elusive. With modern technologies, the functional differences between striosome and matrix compartments are becoming clear. In this review, we summarize the anatomical and functional similarities and differences between the compartments and discuss how compartment-specific circuit function is shaped by neuromodulation. We also point out how technological advances have led to changes in our understanding of striatal compartmental organization and its influence on behavior.

Table 1:

Neuromodulation of Matrix and Striosome Compartments

Neurotransmitter / Receptor	Matrix	Compartmental Bias	Striosomes	References
Acetylcholine	•Multiphasic IPSCs in CINs	>	•Multiphasic IPSCs in CINs	Inoue et al., 2016
	•Monophasic IPSCs in CINs	<	•Monophasic IPSCs in CINs	Crittenden et al., 2017
	•CIN induced pause in SPN spiking	<	•CIN induced pause in SPN spiking	Canales et al., 2000 Crittenden et al., 2017 Salinas et al., 2016
Dopamine	•relative c-Fos expression in response to amphetamine or cocaine	<	•relative c-Fos expression in response to amphetamine or cocaine	
	•Evoked DA release	>	•Evoked DA release	
	•Cocaine ↑ DA overflow	<	•Cocaine ↑ DA overflow	
Glutamate/GABA	•sIPSCs Frequency & Amplitude	=	•sIPSCs Frequency & Amplitude	Smith et al., 2016 Prager et al., unpublished
	•mEPSC Frequency & Amplitude	=	•mEPSC Frequency & Amplitude	
	•NMDA/AMPA Ratios (Proximal & distal spines)	=	•NMDA/AMPA Ratios (Proximal & distal spines)	
μ-opioid receptor	• MOR + DOR expression minimal	<	• MORs in dSPNs & iSPNs, DORs in iSPNs	Miura et al., 2007 Smith et al., 2016 Banghart et al., 2015
	•↓ EPSCs	=	•↓ EPSCs	
	• ENK (leu-ENK) has no effect on IPSCs in dSPNs & iSPNs	<	• ENK ↓ IPSCs (both striosomes & exo-patch neurons) ◆↓ IPSCs mediated by MORs and DORs ◆↓ IPSCs in dSPNs > iSPNs ◆DORs reduce collateral inhibition of dSPNs by iSPNs, subsequently disinhibiting dSPNs	
Substance P	•No change in DA release	<	•↑ DA release in striosome center •↓ DA release in striosome boundaries	Brimblecombe et al., 2015