The Striosome and Matrix Compartments of the Striatum: A Path through the Labyrinth from Neurochemistry toward Function

Katherine R. Brimblecombe* and Stephanie J. Cragg†,‡

†Department of Physiology, Anatomy and Genetics, Sherrington Building, and ‡Oxford Parkinson’s Disease Centre, University of Oxford, Oxford OX1 3PT, U.K.

ABSTRACT: The striatum is a heterogeneous structure with a diverse range of neuron types and neuromodulators. Three decades of anatomical and biochemical studies have established that the neurochemical organization of striatum is not uniformly heterogeneous, but rather, can be differentiated into neurochemically discrete compartments known as striosomes (also known as patches) and matrix. These compartments are well understood to differ in their expression of neurochemical markers, with some differences in afferent and efferent connectivity and have also been suggested to have different involvement in a range of neurological diseases. However, the functional outcomes of striosome—matrix organization are poorly understood. Now, recent findings and new experimental tools are beginning to reveal that the distinctions between striosomes and matrix have distinct consequences for striatal synapse function. Here, we review recent findings that suggest there can be distinct regulation of neural function in striosome versus matrix compartments, particularly compartment-specific neurochemical interactions. We highlight that new transgenic and viral tools are becoming available that should now accelerate the pace of advances in understanding of these long-mysterious striatal compartments.

KEYWORDS: Striosome, matrix, striatum, basal ganglia, dopamine, substance P, acetylcholine, cholinergic interneurons, transgenic tools

UNDERLYING ORGANIZATION OF STRIATUM

The striatum is the primary input nucleus of the basal ganglia and therefore has critical function in motor control and regulation of motivated behaviors.1,2 One of the primary functions of the basal ganglia is the selection of context-appropriate actions.3,4 In order for this to be achieved, inputs must be received, integrated, or segregated from other incoming signals and relayed to appropriate outputs.5 In many areas of the brain, signal processing is facilitated by a highly ordered arrangement of inputs, outputs, and interneurons, for example, into layers.6,7 However, the striatum is a nonlaminar, highly heterogeneous structure with projection neurons (spiny projection neurons, SPNs, also called medium spiny neurons, MSNs) interspersed among a diverse range of interneurons.

Neurons across striatum receive inputs from multiple brain regions including from cortex, thalamus, midbrain, hippocampus, and brainstem.8−15 There is considerable topographic organization, whereby, for example, cortical and dopaminergic inputs from the ventral tegmental area (VTA) and substantia nigra pars compacta (SNc) distribute along a broadly ventromedial to dorsolateral axis.13,11 This topographical organization mirrors functional segregation, whereby dorsolateral striatum and its inputs are typically involved with motor control and ventromedial aspects with associative and limbic functions.13

WHAT ARE STRIOSOMAL AND MATRIX COMPARTMENTS?

Embedded within the topographic organization of the striatum is a histochemically defined organization into two main compartments known as striosomes (also known as patches) and matrix. Striosome−matrix compartments have been described over the past 30 years from immunohistological studies in rat, mouse, tree shrew, cat, ferret, non-human primates, humans, and songbirds, suggesting that the striosome−matrix axis is evolutionarily conserved across birds and mammals and is likely to play an important role in basal ganglia function.14−20 Striosomes form a three-dimensional labyrinth-like structure that interdigitates the matrix. Striosomes occupy 10−15% striatal volume depending on position along the anterior−posterior (AP) and medial−lateral axes.16,21−23 Striosomes have been defined histochemically as expressing high levels of μ-opioid receptor (MOR), substance P (SP), dopamine (DA) 1-receptor (D1R), met-enkephalin (met-ENK), calretinin, Nr4a1, pro-dynorphin, GAD-2, and EGR-1. The extrastriosomal

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matrix by contrast, is enriched with calbindin, somatostatin (SST), enkephalin (ENK), DA2-receptor (D2R), and cholinergic markers including acetylcholine esterase (AChE) and choline acetyltransferase (ChAT) (reviewed elsewhere).\textsuperscript{1,14–16,24–26} Striosomes and matrix compartments have also been suggested to have differing anatomical connections and developmental programs (reviewed elsewhere\textsuperscript{27,28}), and they are differently involved in pathological processes in several psychomotor disturbances that include Parkinson’s disease (PD), Huntington’s disease (HD), attention deficit and hyperactivity disorder (ADHD), and others (reviewed elsewhere\textsuperscript{29}).

Intriguingly, the biochemical composition of striosomes has been suggested to differ with AP coordinate, with MOR expressed at greater density in striosomes found more anteriorly, whereas SP expression is similar throughout the AP axis.\textsuperscript{29} This observation suggests that the composition of striosomes is nonuniform in some attributes, and also that striosome density may have been underestimated from MOR labeling alone at more posterior coordinates.

## DIFFERENTIAL NEUROCHEMISTRY OF STRIosomes AND MATRIX

Despite the characterization of different biochemical markers enriched in striosomes or matrix, the causes and consequences of their divergent expression are not well understood. Specific striatal neuron types can be preferentially distributed with respect to striosomal or matrix compartment.\textsuperscript{15,30} The two classes of SPNs, the D1R- and D2R-expressing SPNs, can reside in either striosome or matrix compartment; therefore both compartments contribute to the direct and indirect output pathways.\textsuperscript{1,32} It is interesting to note that some SPNs respect striosomal boundaries with their dendritic arbors restricted within one compartment, whereas other SPNs appear to disregard these boundaries, and their dendritic arbors span both compartments.\textsuperscript{15} Some classes of striatal interneurons, namely, cholinergic interneurons (ChIs) and calretinin-positive and neuropeptide Y (NPY)-positive GABAergic interneurons, tend to occupy the boundary region between striosomes and matrix, whereas calbindin-positive interneurons show a strong preference for the matrix\textsuperscript{33–35} (Figure 1). What are the outcomes of these compartmental distributions? Do these distributions promote discrete organization of function such as specific interactions between local circuits and thereby provide opportunities to segregate or integrate information processing? Recent studies are now beginning to provide evidence for such functional consequences of striosome–matrix compartmentalization.

The markers that are used commonly to delineate striosome and matrix compartments include striatal neuromodulators, their receptors, or related enzymes, for example, endogenous opiates, SP, D1R, ChAT, and AChE. These observations have recently led us and others to ask the question do the actions of neuromodulators differ between striosome and matrix compartments? One major finding supported by two studies is that DA transmission differs between striosomes and matrix compartments: DA levels are higher in the matrix than in striosomes of dorsal striatum in wild-type mice and in a new transgenic reporter mouse line (Nr4a1−/−eGFP (nuclear receptor subfamily 4, group A, member 1)).\textsuperscript{16,37} These findings indicate an uneven striatal “DA landscape” attributable to striosomes and matrix.

The reasons for nonuniform release of DA between striosomes and matrix are not yet resolved. DA axons innervate both striosomes and matrix compartments, with individual neurons showing different preference for striosome or matrix compartments.\textsuperscript{38,39} But the density of dopaminergic axons is reported to be greater in striosomes than matrix in the rat,\textsuperscript{39} making the finding that DA release is lower in striosomes than matrix appear paradoxical. However, even though it is the striosomes that during development form TH-rich “DA islands”,\textsuperscript{40,41} data from mature cat, non-human primate, and post-mortem human tissue indicate that it is the matrix where TH-immunoreactivity is greater in adulthood.\textsuperscript{23,42} Thus, despite greater axonal density, lower TH levels in striosomes might result in lower DA release. But, DA release levels in adult striatum will not be explained by only innervation density and TH levels but by many other potential contributing mechanisms, whose contributions remain incompletely resolved. For example, the expression and activity of the DA transporter (DAT) will be a major determinant. Lower levels of evoked extracellular DA in striosomes could arise from increased uptake of DA by the DAT, which would be in keeping with findings that striosomes receive more innervation from ventral tier DA neurons of SNc, which express higher DAT mRNA than dorsal tier neurons (which more strongly innervate matrix),\textsuperscript{43} and with the higher DAT immunoreactivity in striosomes.\textsuperscript{36,44,45} However, autoradiographic studies have, conversely, reported lower DAT binding in striosomes.\textsuperscript{46,47} Salinas and colleagues have made a relevant series of observations about DAT function in the Nr4a1−/−eGFP mouse.\textsuperscript{36} They reported striosomal enrichment of DAT-immunoreactivity in dorsal striatum in this mouse, but nonetheless found similar DA uptake kinetic parameters ($V_{max}$ and the decay constants $\tau$) in striosome and matrix compartments. However, cocaine, a DAT inhibitor, had greater effects on...
boosting DA levels in striosomes but apparently greatest effects on dopamine uptake parameters ($K_m$) in the matrix. These effects of cocaine are not straightforward to interpret and could be further complicated by its reported effects as a vesicle mobilizer as well as an inhibitor of uptake, and thus, the mechanisms are incompletely understood. Salinas and colleagues have speculated that lower DA release levels in striosomes and greatest enhancement by cocaine might reflect differences in DA fibers that impact on vesicle recruitment or distribution. Intriguingly, these compartment-specific effects of cocaine were not seen in the ventral striatum, suggesting that mechanisms linked to the DAT cannot underlie differences in DA release levels between compartments for all the striatum. In any event, potential differences in vesicular distribution, DAT function, or the action of cocaine between striosomes and matrix that are indicated by these studies could have important implications for DA signal transduction and also for the effects of psychostimulants cocaine and amphetamine.

DA levels will also be strongly influenced by other neuromodulators, which might also be expected to display striosome—matrix differences. ACh is a powerful presynaptic modulator of striatal DA release, maintaining high initial release probability and clamping re-release and also directly driving DA release, via striatal nicotinic receptors (nAChRs). AChE is found at higher levels in matrix, which hypothetically could give rise to differential ACh levels between striosomes and matrix. Lower AChE levels in striosomes could be a surrogate marker for low ACh innervation density and low ACh levels, but alternatively, low AChE levels could limit ACh hydrolysis resulting in paradoxically higher ACh levels. However, a differential control of DA by ACh is not supported by a recent study in the Nra41−eGFP mouse, which indicated that ACh modulates DA release via nAChRs similarly in striosomes and matrix (Figure 2).

It is currently unclear whether ACh itself displays variable levels in striosomes versus matrix. However, in accordance with higher expression of cholinergic markers in matrix, it has recently been found that there is more nAChR-dependent modulation of Chls by SPNs in matrix than striosomes. This is thought to indicate that ACh released from Chls acts upon nAChRs on SPNs in the matrix preferentially, stimulating GABA release, which feeds back onto Chls. These findings also suggest that there is significant scope for ACh to have compartment-specific outcomes on striatal function (Figure 2). In addition, it should also be noted that during late embryonic and early postnatal development, the striatal DA islands, which go on to become striosomes in adulthood, are AChE-rich, and only switch to being AChE-poor in adulthood. It remains to be understood how or why striosomes switch from AChE-rich to AChE-poor and what signaling implications for ACh might also result.

The neuropeptide SP also has significant scope for compartment-specific function, including an action on DA transmission. SP is produced and released by D1R-expressing MSNs and is enriched in the striosomes. Neurokinin-1 receptors (NK1Rs), which are the principal target receptor for SP, are expressed throughout the striatum but somewhat paradoxically are at higher density in the matrix, predominantly on nitric-oxide synthase-expressing GABAergic interneurons (NOS interneurons), somatostatin-positive interneurons (SST-positive), and Chls. This mismatch in expression between SP and its NK1R has also been reported in other brain regions and likely reflects a role of SP as a volume transmitter with actions at sites remote from release. SP is not known to be taken back up into neurons, and no SP-specific peptidase has yet been identified that could catabolize SP to limit the spread of its function (although AChE has been shown to hydrolyze SP in vitro).

We recently revisited the action of SP on striatal DA to explore whether previous contradictory findings could be attributed to a striosome—matrix compartmentalization. SP has historically been shown to have a range of possible outcomes on striatal DA release, and we reconciled this conflicting literature by revealing that SP has variable effects on DA release depending location along striosome—matrix axis. SP increases DA release in striosomes, decreases DA release at striosome—matrix boundaries, and has no effect in the surrounding matrix. These data show that DA release can be under different control mechanisms between striosome and matrix compartments. The outcome of SP on DA release is a “weighted DA signal” that varies relative to striosome—matrix positioning (Figure 2). This weighting of DA signals in striosomes versus matrix could have important implications for striatal output and opens the door to the question of whether other neuromodulators might also modulate this “DA landscape” along a striosome—matrix axis.

There is large scope for other neuromodulatory peptides to have nonuniform effects on striatal function between striosome and matrix, due to their differential expression between these regions. ENK has been found to disinhibit MSNs in striosomes, particularly direct pathway neurons, despite ENK itself being
enriched in the matrix.\textsuperscript{69} In addition, re-expression of MOR in striosomal D1R-SPNs selectively restores the rewarding but not addictive properties of opiates.\textsuperscript{70} These examples of the compartment-specific/favoring effects of neuromodulators indicate not only compartment-specific function but also that neuromodulators can signal between compartments in a manner that is not obvious from receptor localization.\textsuperscript{37,69} Many striatal neuromodulators might signal via volume transmission rather than classical synaptic transmission, which may explain the lack of fidelity between their site of production compared to their predominant receptor location.\textsuperscript{71,72}

Calbindin is a well reported marker of the matrix and is expressed by several cell types including SPNs that occupy the matrix, calbindin-positive GABA interneurons in the matrix, and dopaminergic axons from VTA and dorsal SNc that preferentially project to the matrix.\textsuperscript{54,73} It is intriguing that so many different cell types show calbindin enrichment in the matrix, but whether this has any significance, for example, for developmental mechanisms, signaling, or degeneration in disease, is debated but unresolved.\textsuperscript{34,54,81,82}

\section*{\textbf{SEGREGATED SIGNALING OR INFORMATION TRANSFER?}}

There is evident scope for compartment-specific modulation of function, which might differently weight signal processing in each compartment. But these findings also suggest a degree of crossover of function between each compartment, with modulators enriched in one zone apparently able to influence neuronal function in another. Thus, compartment-specific modulation can be intercompartmental. To what extent could striosome and matrix compartments be designed to interface and interact? This is an intriguing area that is beginning to receive attention.

Data from recordings in SPNs suggest that SPNs for the most part do not interact directly between compartments.\textsuperscript{69,75} Lopez-Huerta et al. propose the idea of the striatum being “one structure—two entities” regarding the lack of information transfer between SPNs in matrix and striosome compartments. This is in broad agreement with the limited collaterals from SPNs in matrix that functionally innervate striosomal SPNs and vice versa\textsuperscript{15,69} (Figure 2). However, structural data indicate that some SPNs do cross striatal borders.\textsuperscript{15} It would be interesting to identify whether these cells have specific markers to help their function, including whether they might mediate information transfer between regions.

Some striatal neurons have been proposed to mediate information transfer between striosomes and matrix compartments (Figure 2). In particular, Chls and also SST-positive (“LTS neurons”) GABA interneurons are often noted to reside at the interface between striosomes and matrix.\textsuperscript{15,33} Until recently, Chls were thought to reside only in the matrix, extending processes only sparsely into striosomes but profusely into the matrix,\textsuperscript{35} but more sensitive labeling techniques exploiting ChAT−ChR2 BAC transgenic and ChAT−Cre knock-in mouse lines have revised this view. They have identified that Chls can be found occasionally in striosomes (identified by poor expression of matrix marker CalDAG−GFP) and that while thicker putative cholinergic dendrites are more prevalent in the matrix, leading to apparent enrichment of the matrix in cholinergic fibers, the finer processes with varicosities assumed to be axons are dense in both the matrix and striosomes.\textsuperscript{74} Amemori and colleagues’ propose that information transfer between striosomes and the surrounding matrix via such critically located interneurons could promote action selection by facilitating the direct pathway of the basal ganglia. They refer to this process as a “high responsibility signal” that is activated when an action is deemed appropriate. Conversely when an action is deemed inappropriate they propose that there is limited information transfer between striosomes and matrisomes (the local associated module of matrix),\textsuperscript{75} which results in a “low responsibility signal” and an action being avoided. The Amemori model is consistent with findings that when Chls are upregulated, animals develop stereotypies, which could be due to excessive information flow between striosomes and matrisomes by Chls generating an erroneous “high responsibility signal.”\textsuperscript{76} Conversely when striosomes are ablated, which presumably decreases information flow between striosomes and matrisomes, it prevents the acquisition of cocaine-induced stereotypies.\textsuperscript{77}

Friedman et al.\textsuperscript{78} provide key evidence for compartment-specific functions of striosomes versus matrix that also implicate a key role for striatal interneurons. By optogenetically tagging striosome-prefering or matrix-prefering prefrontal cortical inputs to dorsomedial striatum (from prelimbic versus anterior cingulate cortex respectively), they showed that striosome-prefering inputs selectively are active during cost–benefit tasks and appear to activate intrastriatal inhibitory interneurons that inhibit striosomal SPNs. These findings suggest that intrastriatal networks connecting cortical inputs to striosomes might play a particularly important role in decision-making during conflicting motivational demands, with significant implications for our understanding of many aspects of both normal and pathological behaviors.

There is scope for different control mechanisms in striosomes and matrix to influence not just intrastriatal circuitry but also striatal output from each compartment. Furthermore, if SPNs in striosomes provide greater reciprocal innervation of dopamine neurons than those in matrix, then striosomal mechanisms might be particularly important for modifying striato–nigro–striatal loops.\textsuperscript{11,32,39,79,80}

\section*{\textbf{TWO, THREE, OR MORE COMPARTMENTS? BEYOND STRIOSOMES AND MATRIX}}

Observations reported from the 1980s onward have also described biochemical characteristics of a potential third neurochemically defined compartment, in addition to the striosomes and matrix. This third compartment has taken the form, using a variety of markers, of a ring around striosomes at their interface with the surrounding matrix. A ring zone has been observed in different studies to have either high met-ENK expression, high SP expression with strong overlap with NK1R density, or high density of interneuron soma, especially Chls, SST-positive, and calbindin-positive.\textsuperscript{34,54,81,82} This ring zone around the striosomes has been variously termed an annulus, a peristriosomal region, a striocapsule, and boundary region. It is not yet known whether a common zone has been identified in these different studies.

Recent experimental evidence has provided renewed insight into such a third annular compartment. Until recently, there was no evidence that this “peristriosomal” region could be defined functionally. However, we were able to show that DA release at the boundary region between striosomes and surrounding matrix was decreased by SP, while by contrast, DA release within striosomes was increased, and that in the matrix was unmodified\textsuperscript{37} (Figure 2).
Very recently, the striatal striosome (or “patch”) compartment has been suggested to include a subset of striatal SPN neurons in the matrix, named “exo-patch” SPNs. Smith et al.32 exploited the Sepw1-/-NP67-/-Cre mouse line, which when injected with viral Cre-dependent GFP and Td-Tomato constructs demonstrates fluorophore expression that correlates with high MOR immunoreactivity, that is, in presumed striosomes. In this line, a population of SPNs were found to reside in the presumed matrix but to have neurochemistry, connectivity, and electrophysiological characteristics resembling striosome (patch) neurons. It is not yet known whether “exo-patch” neurons are found across mouse lines and species or using other markers.

It is of note that the majority of work investigating striosome and matrix compartments has focused on the dorsal striatum. However, there is also a striosome/matrix neurochemical heterogeneity in the ventral striatum including the nucleus accumbens. In mouse ventral striatum, MOR and calbindin immunoreactivity show heterogeneity, in swirl-like patterns rather than the distinctive “patches” seen in dorsal striatum. There is also evidence to indicate that SPNs in calbindin-poor areas (striosomes) of ventral striatum innervate DA neurons in the VTA, analogous to the reported innervation of SNC by striosomal SPNs in the dorsal striatum. However, in contrast to the dorsal striatum, where striosomes display lower levels of DA release than the matrix, in the ventral striatum, the relationship is inverted, with greater DA release in striosomes. The explanation and consequences for striosome-matrix signal integration in ventral versus dorsal striatum are unresolved and ripe for investigation.

### NEW TOOLS FOR INVESTIGATING THE FUNCTIONS OF STRIOSOMES, MATRIX, AND OTHER COMPARTMENTS

Research into the divergent functions of striosomes and matrix (and other compartments) has to date been hindered by the technical challenges involved in identifying the location of each compartment during specific experimental manipulations. Until recently, it was only possible to confirm striosome and matrix locations after experimentation using histochemical or immunochemical approaches, limiting the avenues of possible experiments and their yield. However, this is all about to change. The advent of new genetic technologies has begun to revolutionize the study of the function of striosomes and matrix and will continue to do so as new transgenic mice and other strategies become more widely available.

Mainstream immunocytochemical approaches, for example, only reveal striatal compartment after fixation. Experiments need to be done blind with respect to striosome-matrix location, the recording sites need to be marked and then localized with reference to a striosome-matrix marker after postfixation immunolabeling. The process is time-consuming, and the data yield is inevitably lower in the smaller volume compartment, the striosomes, which will be sampled less frequently. Immunochemical approaches can also be replete with technical hazards. For example, ENK, pro-ENK, and met-ENK can differentially signify matrix or striosomes depending on the immunochemical method used. These challenges can be overcome with new transgenic mice that permit direct visualization of striosomes or matrix compartments including during experiments on acutely living ex vivo tissue. The US National Institute of Health (NIH)-funded initiative, the gene expression nervous system atlas (GENSAT), has generated transgenic mouse lines by using bacterial artificial chromosome (BAC) to drive enhanced green fluorescent protein (eGFP) expression using the promoter elements of specific endogenous genes. A number of these mouse lines have fortuitously now been characterized as having preferential eGFP expression in either striosome or matrix subdivisions. As a result, these transgenic lines offer the convenient ability to identify striatal compartment during experimental investigation thus enabling direct experimental investigations in identifiable compartments. Some better characterized lines are Nr4a1-eGFP, PDYN-eGFP, and Sepw1-/-NP67-/-Cre mouse lines, which show enriched eGFP or Cre expression in striosomes, and Plxnd1-/-OG1-/-Cre line, which shows Cre expression in matrix. Striosome- or matrix-specific Cre-driver lines can be used to visualize compartments when mice are injected with Cre-dependent virally packed constructs containing fluorophores, for example, AAV-tdTomato, or are crossed with transgenic mice expressing Cre-dependent fluorophores under a ubiquitous promoter, for example, Ai14 line. Additionally, specific Cre lines allow for the expression of light-activated ion channels to be targeted to either striosome or matrix compartments, allowing not only for visualization of each compartment but also their activation or inhibition. The ability to activate or inhibit striosome or matrix regions selectively and in vivo is the technical innovation the field needs to overcome previous technical limitations in understanding of the function of these different compartments. Recent studies using these approaches have already begun to transform understanding and now pave the way for future research.

These new mouse lines could and should revolutionize the study of the function of striosomes and matrix but are not without their caveats. GENSAT ensured the fidelity of the eGFP expression compared to endogenous genes by comparing multiple lines and in situ hybridization from wild-type animals. But despite the pattern of gene expression being confirmed, eGFP expression may not perfectly reflect endogenous genes over certain time periods due to differences from the endogenous protein in stability and half-life. Fortunately, in many cases, any disparity between driver gene and fluorophore expression will not diminish the usefulness of these lines for identifying specific cells of interest, but care should be taken when these lines are used to investigate how specific genes control striosome and matrix formation. This will be particularly of relevance when studies are probing developmental patterns or if striosome/matrix patterns are not static but dynamically vary over short time periods, for example, throughout circadian rhythms. Therefore, it is of great importance to thoroughly characterize transgenic lines of interest and replicate findings in multiple lines, as well as to corroborate in wild-type animals where possible.

To date BAC transgenic lines for live visualization of striosomes or matrix are only available in mouse. Future developments may extend these technologies into rats. With the ever increasing use of CRISPR, there may well also be scope to generate eGFP knock-in lines in a wider range of species to further enhance cross-species validation. Further advantages of CRISPR/cas9 mediated knock-in strategies are that they often result in less variability of expression compared to BACs where copy number integration is unpredictable. However, knock-in strategies may not always result in sufficient fluorophore expression for in vivo use, illustrating the need for a range of transgenic techniques with different advantages.
There are also alternatives to genomic-encoded florescent proteins to visualize striatal compartment. It was recently found that AAVrh10 preferentially transfects SPNs in matrix rather than SPNs in striosomes.\textsuperscript{75} Striatal interneurons appeared to be targeted regardless of their location. The reason for the preferential targeting of matrix neurons by AAVrh10 is currently unknown, but this targeting could be of huge significance since AAVrh10 is currently the serotype of interest for transgene delivery in the treatment of a number of neurodegenerative disorders including Parkinson’s disease, which has also been associated with imbalances between striosome and matrix compartments.\textsuperscript{3,24,30,88} Viral technologies may therefore offer the ability to target striosomes and matrix not just for experimental investigation but also for neural therapies.

An alternative method to probe striosomal function has been to selectively ablate striatal neurons using MOR-targeting toxin. The ablation of MOR-rich neurons has illustrated the importance of striosomes for learning certain motor behaviors and also their role in the acquisition of cocaine induced stereotypies.\textsuperscript{7,20,90}

An additional original approach used to target striatal compartments in order to identify compartment function has exploited the differences in inputs to striosomes and matrix. Friedman et al.\textsuperscript{78} targeted inputs to striosomes or matrix regions by virally transfecting prelimbic cortex (PL) or anterior cingulate cortex (ACC), respectively, with eYFP–halorhodopsin or –C1V1 to optogenetically inhibit and activate transfected neurons, respectively. This approach resulted in over 5-fold higher expression of transfected eYFP in striosomes (confirmed by MOR-immunostaining) after PL injection and over 2.5-fold higher expression in matrix after ACC injection sites. This anatomical strategy for targeting striosomes or matrix is a valuable additional approach to the emerging development of genetic driver lines. We must be cautious to not rely on a single genetic tool or rodent model, which all come with their own quirks and anomalies, to ensure we are identifying functions irrespective of animal line or labeling method.

\section*{CONCLUDING REMARKS}

There is ever increasing interest in understanding the function of the striosome-matrix axis of the striatum. Newly emerging evidence suggests that there are identifiable functional outcomes of this compartmentalization, such as discrete neurochemical interactions within or between compartments, leading to spatial weighting and regulated communication. There is also evidence for additional compartments, such as peristriosomes. The implications for striatal function of these two, three, or more compartments are however still to be identified. New transgenic and viral tools are finally becoming available that have great potential to overhaul our limited understanding of the functions of striosomes and matrix and to shed light on implications of striatal compartmentalization for information processing in the striatum and the functions of the basal ganglia.

\section*{AUTHOR INFORMATION}

\textbf{Corresponding Author}

*Dr. Katherine R. Brimblecombe. E-mail: Katherine.brimblecombe@dpag.ox.ac.uk.

\textbf{ORCID}

Katherine R. Brimblecombe: 0000-0003-0809-7292

Stephanie J. Cragg: 0000-0001-9677-2256

\section*{Notes}

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