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Thalamostriatal projections and striosome-matrix compartments

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ABSTRACT

The neostriatum has a mosaic organization consisting of striosome and matrix compartments. It receives glutamatergic excitatory afferents from the cerebral cortex and thalamus. Recent behavioral studies in rats revealed a selectively active medial prefronto-striosomal circuit during cost-benefit decision-making. However, clarifying the input/output organization of striatal compartments has been difficult because of its complex structure. We recently demonstrated that the source of thalamostriatal projections are highly organized in striatal compartments. This finding indicated that the functional properties of striatal compartments are influenced by their cortical and thalamic afferents, presumably with different time latencies. In addition, these afferents likely support the unique dynamics of striosome and matrix compartments. In this manuscript, we review the anatomy of basal ganglia networks with regard to striosome/matrix structure. We place specific focus on thalamostriatal projections at the population and single neuron level.

1. Introduction

Neurons in the striatum do not form a layered or columnar structure as seen in the cerebral cortex and cerebellum. Although striatal neurons appear to be randomly distributed, they are actually separated into two distinct compartments called striosomes (patches in rodents) and matrix. The dopaminergic axons innervated the patchy 'dopamine islands' more densely than surrounding 'matrix' in rat caudate putamen (CPu) transiently during the first 2 weeks after birth (Song and Harlan, 1993). The matrix eventually comprises approximately 85% of the entire striatum (Johnston et al., 1990; Nakamura et al., 2009). Acetylcholinesterase, calbindin, and somatostatin are strongly expressed in the matrix compartment (Graybiel and Ragsdale, 1978; Gerfen and Scott Young, 1988; Gerfen, 1992), while the striosome is rich in μ-opioid receptors (MOR) (Delfs et al., 1994; Mansour et al., 1994, 1995; Minami et al., 1994; Arvidsson et al., 1995; Kaneko et al., 1995; Nakamura et al., 2009).

Striosome neurons in the CPu project to the substantia nigra pars compacta (Gerfen, 1985; Jimenez-Castellanos and Graybiel, 1987; Nambu et al., 2002; Lévesque and Parent, 2005; Fujiyama et al., 2011; Watabe-Uchida et al., 2012; Crittenden et al., 2016). Matrix neurons send projections to GABAergic neurons in the substantia nigra pars reticulata (SNr) (Castel et al., 1993; Lévesque and Parent, 2005; Watabe-Uchida et al., 2012), although the question is still open to argument whether the matrix neurons also innervate dopaminergic neurons (Smith et al., 2016). Mesencephalic dopamine neurons show complex reward-related responses (Schultz et al., 1998; Schultz, 2007a, b); therefore, striosome and matrix compartments are thought to play different roles in reinforced learning of the basal ganglia. Houk et al. suggested that role sharing occurs in the striatum during reinforcement learning, with particular focus on the striosome/matrix compartments. According to the model, action selection occurs in the matrix, through the basal ganglia output nuclei [the internal segment of the globus pallidus (GPi)/SNr] (actor). Reward prediction (critic) takes place in the striosomes. Projections that target dopaminergic neurons calculate reward prediction errors, and actor–critic learning is processed by dopaminergic projections to the striatum (Houk et al., 1995).

The striatum receives excitatory glutamatergic afferents from the cerebral cortex and thalamus (Smith and Bolam, 1990). Striosome neurons receive cortical inputs primarily from the orbitofrontal cortex and insula of the limbic cortex (Crittenden and Graybiel, 2011). However, the matrix receives input from a wider area of the neocortex, including the motor cortex, somatosensory area, and parietal lobe in the primate (for review, see Crittenden and Graybiel, 2011), rat (Gerfen, 1984, 1989; Donoghue and Herkenham, 1986) and cat (Malach and Graybiel, 1986; Ragsdale and Graybiel, 1991). The striosome and matrix compartments are also innervated by projections from specific cortical layers. In rats, the matrix receives input from cortical layers 3 and 5a, while axons from layers 5b and 6 project to the striosomes, although recent report using transgenic mice showed no difference in

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the cortical areas or layers between the striatal compartments (Smith et al., 2016). Striatal subregions containing both striosome and matrix compartments are innervated by the related cortical regions (Kincaid and Wilson, 1996). Pathway-specific optogenetics and electrophysiological studies have revealed a selectively active medial prefronto-striosomal circuit during cost-benefit decision-making under approach avoidance conflict conditions in rats (Friedman et al., 2015).

Therefore, the striatum has a mosaic organization and the different compartments are distinguished by their cortical input and striatofugal output (for review, cf. Johnston et al., 1990; Crittenden and Graybiel, 2011). However, how the thalamostriatal projections differ in the striosome and matrix has not been clarified. In this manuscript, we review our current understanding of basal ganglia anatomy and striosome/matrix networks. In particular, we focus on thalamostriatal projections at the population and single neuron level.

1.1. Thalamostriatal neurons project predominantly to the matrix compartment

We previously reported that the vesicular glutamate transporter 1 (VGluT1) and VGluT2 were expressed in corticostriatal terminals and thalamostriatal terminals, respectively (Fujiyama et al., 2001, 2004; Kaneko and Fujiyama, 2002; Kaneko et al., 2002). *In situ* hybridization revealed high levels of VGluT1 mRNA, but not VGluT2 in layers 5 and 6 of the cerebral cortex (Hisano et al., 2000; Fremeau et al., 2001). In contrast, thalamic nuclei strongly expressed VGluT2, but not VGluT1 (Herzog et al., 2001; Fremeau et al., 2004; Moutsimilli et al., 2005). However, some studies reported that VGluT1 mRNA has been detected in some thalamic neurons (Fremeau et al., 2004; Barroso-Chinea et al., 2008). On the other hand, when thalamic neurons in the ventrobasal thalamic nuclei were chemically ablated, most of the VGluT2 immunoreactivity disappeared from the primary sensory cortex, while VGluT1 immunoreactivity did not change significantly (Fujiyama et al., 2001). Furthermore, in the cerebral cortex, VGluT2 mRNA is weakly expressed only in layer 4 (Hisano et al., 2000); however, layer 4 neurons never project to subcortical regions such as the striatum (Lorente de Nó, 1992). Recent studies with transgenic animals suggest that the subpopulation of VGluT2 expressing neurons in the cortex, hippocampus and amygdala may contribute some aspects of cognitive function (Wallen-Mackenzie et al., 2009; He et al., 2012). Our anterograde tracing study with VGluT immunoreactivity revealed that almost all labeled corticostriatal terminals express VGluT1 (Fujiyama et al., 2004). These findings revealed that VGluT1 and VGluT2 represent markers for corticostriatal and thalamostriatal terminals, respectively.

Quantitative analysis of VGluT1 immunostaining showed no statistical differences between the striosome and matrix compartments (Fig. 1) (Fujiyama et al., 2006). In contrast, VGluT2 immunostaining was clearly weaker in striosomes compared with the matrix compartment (Fig. 1) (Fujiyama et al., 2006). Striosome/matrix ratios of VGluT2 expression were approximately one-third lower than those for VGluT1, which were near 1.0. These findings indicated that VGluT1-positive axon terminals (probably whole corticostriatal axon terminals) are distributed almost evenly between striosome and matrix compartments. In contrast, VGluT2-positive axon terminals (probably thalamostriatal axon terminals) are more predominant in the matrix.

1.2. Differences in the synaptic organization of cortico- and thalamo-striatal terminals between striatal compartments

As concerned with the cortical inputs, previous ultrastructural studies combined with anterograde tracing have revealed that corticostriatal afferents primarily formed synapses with dendritic spines in the striatum of cat (Kemp and Powell, 1971; Frotscher et al., 1981), monkey (Smith et al., 1994) and rat (Hattori et al., 1979; Somogyi et al., 1981; Dubé et al., 1988; Xu et al., 1989; Wictorin et al., 1989; Wilson et al., 1990; Hersch et al., 1995). We and others found that more than 80% of VGluT1-immunopositive terminals (likely of cortical origin) form axospinous synapses rather than direct axodendritic synapses in the striatum by combining morphological analyses with VGluT1 immunoreactivity (Fujiyama et al., 2006; Raju et al., 2006; Lei et al., 2013). On the other hand, a considerable number of contralaterally projecting corticostriatal terminals have been reported to form the synapse with dendritic shafts in cat (Kemp and Powell, 1971). Also as for the corticostriatal projections originating in the motor cortical area in rats, a much higher proportion of contralateral corticostriatal synapses were with dendritic shafts (30%) than ipsilateral corticostriatal synapses (4%) (Hersch et al., 1995). Therefore, almost all ipsilateral corticostriatal projections formed synapses with spines while many contralateral corticostriatal projections formed synapses onto dendritic shafts.

As for the thalamic terminals, previous studies of synaptic organization using VGluT2 immunoreactivity have found that thalamic terminals are more often on dendritic shafts than are cortical terminals, although there is considerable study-to-study variation in frequency (Fujiyama et al., 2006; Raju et al., 2006; Lacey et al., 2007; Lei et al., 2013). However, some afferents from rostral intralaminar (IL) thalamic nuclei synapse with dendritic spines (Xu et al., 1989; Ichinohe et al., 2001). As for the striatal compartments, VGluTs staining revealed differences in the synaptic organization of thalamostriatal neurons between the striosome and matrix (Fujiyama et al., 2006; Raju et al., 2006). We quantitatively analyzed ultrastructural images and revealed that 84% of thalamostriatal projections synapsed on dendritic spines in striosomes, whereas 70% synapsed on dendritic shafts in the matrix compartment (Fig. 2). Furthermore, thalamostriatal axospinous synapses in striosomes were larger than corticostriatal axospinous synapses in either compartment (Fujiyama et al., 2006).

It has been reported that excitatory glutamatergic axospinous synapses, including corticostriatal axospinous synapses, often display a high degree of synaptic plasticity (Calabresi et al., 2000). Furthermore, Yuste and Bonhoeffer reported that dendritic spines rapidly and frequently change their form, presumably reflecting their plasticity (Yuste and Bonhoeffer, 2001). These previous reports suggest that

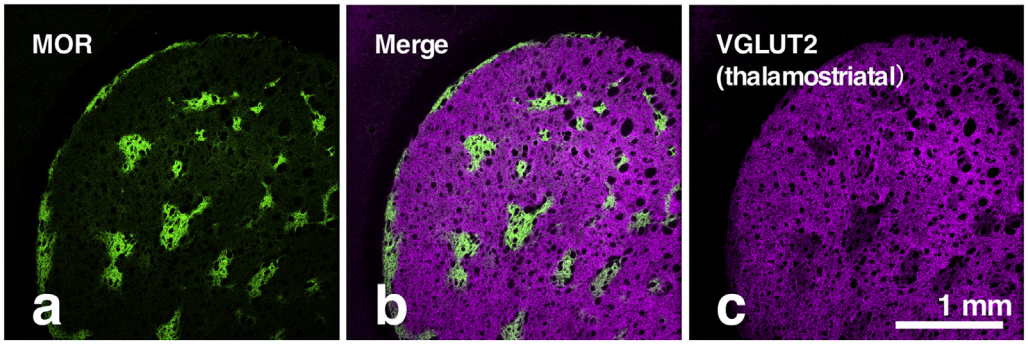

Fig. 1. Cortical–thalamic input and striosome–matrix structure [from (Fujiyama et al., 2006) with modifications]. Double immunofluorescence images for μ-opioid receptor (MOR) and VGluT2 in the neostriatum. Intense MOR staining in the patch compartment corresponded to areas that were weak in VGluT2 immunoreactivity (a, b, and c). MOR, μ-opioid receptor; VGLUT2, vesicular glutamate transporter 2.

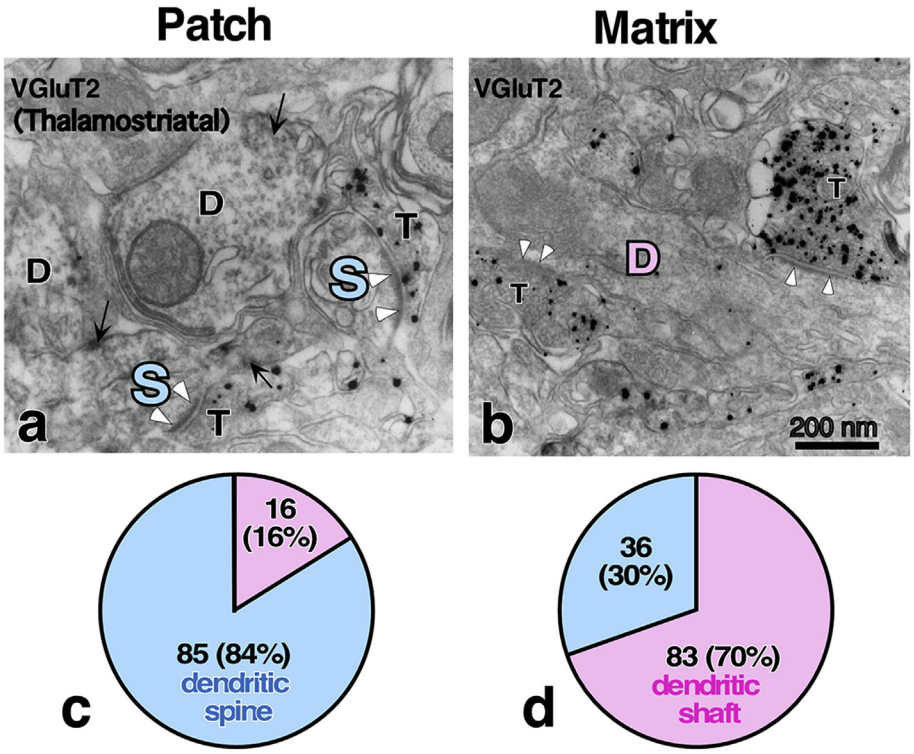

Fig. 2. VGluT2-immunopositive synapses in the patch and matrix compartments. (a), VGluT2-positive terminals (T, silver grains) formed asymmetric synapses (white arrowheads) with dendritic spines (S), and occasionally with dendritic shafts (D in a). DAB reaction product (arrows) indicating MOR immunoreactivity was observed in dendritic profiles, indicating that the examined regions were within the patch compartment. (b), in matrix, VGluT2-positive terminals (T, silver grains) made asymmetric synapses (white arrowheads) mainly with dendritic shafts (D in b) containing mitochondria, and occasionally with dendritic spines. Scale bars = 200 nm in b (applies to a). Pie charts displaying the proportions of dendritic spines (c) vs. shafts (d) postsynaptic to VGluT2-imunopositive terminals in striosomes and matrix, respectively (Fujiyama et al., 2006).

thalamostriatal synapses on dendritic shafts in the matrix are less plastic than those on dendritic spines in the striosome compartment and also less plastic than corticostriatal axospinous synapses. Considering with Houk's model, the plastic axospinous synapses in the striosome originating from both cortex and thalamus can contribute to efficient reward prediction. Moreover, postsynaptic differences between thalamostriatal projections in the striatal striosome and matrix compartments may reflect the functional difference in synaptic plasticity and/or cell type that is targeted.

1.3. Thalamic subnuclei and striosome/matrix compartments

Thalamic projections primarily arise from the IL and midline (ML) thalamic nuclei (Bentivoglio et al., 1991; Groenewegen and Berendse, 1994; Mengual et al., 1999; Van Der Werf et al., 2002). In the basal ganglia, the principal target of ML neurons is the nucleus accumbens (NAc) and olfactory tubercle, whereas for IL neurons it is the CPu, or dorsal striatum. In rodents, the IL consists of the central medial (CM), central lateral (CL), paracentral (Pc), and parafascicular nuclei (Pf); the former three nuclei are collectively named “the rostral group of the IL (ILr)” in this review. The ML is composed of the paraventricular (Pv), rhomboid (Rh), reuniens (Re), intermediodorsal (IMD), and paratenial nuclei (Pt), although the Rh is sometimes included in the IL and the Pv in the epithalamus (cf. Jones, 2007).

We reconstructed ML, ILr, and Pf neurons and found that they were multipolar with many dendrites. ILr neurons had many short radiating dendrites, extending to about 300–400 μm in diameter. In contrast, Pf neurons had fewer, more widely extended dendritic branches (≥500 μm). ILr neurons were classified as “bushy” relay neurons, whereas Pf neurons were termed large “reticular-like” neurons, as reported previously (Deschenes et al., 1996; Lacey et al., 2007; Unzai et al., 2017). Our findings were consistent with a recent finding that one-third of neurons in the lateral Pf had bushy dendrites and extended type I axons in the CPu, while the remaining neurons had reticular-like dendrites and projected type II axons (Beatty et al., 2009). The dendrites of ML neurons were less bushy and more widely spread than ILr neurons, but were not as “reticular-like” as Pf neurons. Thus, the ML neurons were not classified as type I or type II cells as previously described (Deschenes et al., 1996). Since the rat ML is known to receive information from the hypothalamic nuclei, periaqueductal gray, deep mesencephalic reticular formation, parabrachial nuclei, and nucleus of the solitary tract, ML seem to be associated with autonomic or visceral functions (Cornwall and Phillipson, 1988; Krout and Loewy, 2000; Krout et al., 2002). In contrast, IL were suggested to convey multimodal sensory-driven signals (Grunwerg and Krauthamer, 1992; Matsumoto et al., 2001; Minamimoto and Kimura, 2002). Previous studies of thalamic nuclei have shown that IL neurons project axons preferentially to the matrix compartment (Herkenham and Pert, 1981; Sadikot et al., 1990, 1992; Ragsdale and Graybiel, 1991). Furthermore, the striosome compartment receives input from ML neurons located at the Pv and Rh in the cat (Ragsdale and Graybiel, 1991). In addition, the striosome compartment in the rat NAc is innervated by the Pv (Berendse et al., 1988). Differences have been reported in the post-synaptic structure (dendritic shaft *vs.* spine) synapsed by thalamostriatal axons between the striosome and matrix (Fujiyama et al., 2006; Raju et al., 2006). Differences have also been described in dendritic and axonal morphologies between CL and Pf neurons (Pinault, 1996; Lacey et al., 2007). These findings suggest that thalamic subnuclei are heterogeneous for projection to striatal striosome and matrix compartments.

To elucidate how the striatal compartments are innervated by thalamostriatal projections, we examined these projections in individual ML and IL neurons. We investigated the axonal trajectory visualized with viral vectors expressing membrane-targeted fluorescent proteins in the striosome/matrix organization and NAc defined with MOR immunoreactivity in rats (Unzai et al., 2017). Additionally, we investigated how single thalamostriatal neurons innervated cortical and subcortical regions (Unzai et al., 2017). The thick non-varicose axons of the 15 ML neurons heading towards the forebrain passed through the internal capsule, frequently emitting axon collaterals to the striatum (12/15 neurons), and subsequently entered various cortical areas, including the medial prefrontal, orbitofrontal, and insular areas (Unzai et al., 2017). Pv neurons, and to a lesser extent Rh and Pt neurons, sent axon varicosities to the CPu with a clear preference for the striosome compartment (Unzai et al., 2017). This is consistent with previous

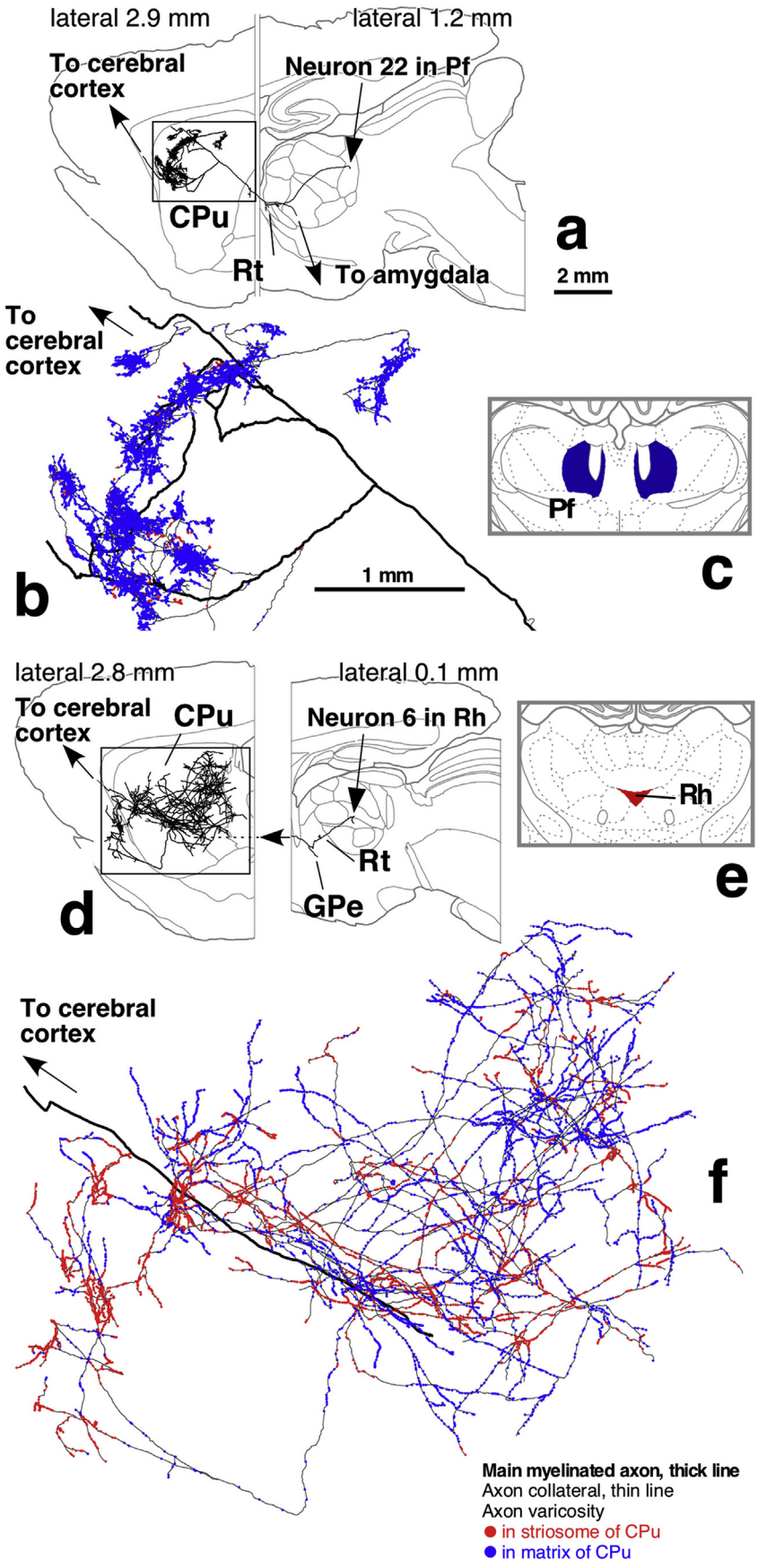

Fig. 3. Reconstruction of the thalamostriatal axons of Pf and ML neurons [from Unzai et al. (2017) with modifications]. A neuron (a) in Pf (c) emitted type II axon fibers mostly to the matrix compartment of the CPu. The axon fibers were often clustered locally, and some neurons formed multiple clusters of axon varicosities (a, b). In high magnification reconstructions of the striatal axons (b), the clustered axons contained en passant and terminal boutons. Furthermore, axon varicosities were mostly distributed in the matrix compartment (blue varicosities in b). A neuron (d) located in the Rh (e) emitted widespread type I axon collaterals in the CPu (d, f). In high magnification reconstructions of the striatal axons, axon varicosities were distributed preferentially in the striosome compartment (red varicosities) (f). Scale bar in (a) also applies to (d), and (b) applies to (f).

findings that Pv and Rh neurons preferentially innervated the striosome in the cat brain (Ragsdale and Graybiel, 1991). Furthermore, Pv, Rh, and Pt neurons preferentially innervated MOR(+) regions in the NAc (Unzai et al., 2017). In contrast, each one case of Re and IMD neurons did not show a preference for innervating the striosome compartment; 12% of striatal axonal boutons derived from Re neurons and 7.3% of striatal axonal boutons derived from IMD neurons innervated the striosome, although each one case was examined in this study (Unzai et al., 2017).

In our study, the intrastriatal axon collaterals of six ILr and five Pf neurons were analyzed at the single neuron level. All except one IL neuron emitted axon collaterals in the striatum and innervated cortical areas including motor, somatosensory, cingulate, retrosplenial, orbital, and/or insular areas (Unzai et al., 2017). Previous anterograde labeling studies with conventional tracers revealed that the neurons in the cat and monkey CM-Pf complex selectively innervated the acetylcholinesterase-rich matrix compartment (Sadikot et al., 1990, 1992; Ragsdale and Graybiel, 1991). The CM-Pf corresponds to the Pf of rat thalamic nuclei (for review, cf. Jones, 2007), and rat Pf neurons project mainly to the acetylcholinesterase-rich matrix compartment (Herkenham and Pert, 1981). Our single neuron tracing study also revealed that all five of the Pf neurons projected to the CPu, and four of them projected preferentially in the matrix compartment. In contrast to the ML neurons, our description of axonal arborization of individual Pf neurons also revealed that the striosome targeting proportion of Pf neurons was much smaller. We further demonstrated that intrastriatal axon collaterals of ILr neurons are not biased toward the matrix or striosome compartment (Unzai et al., 2017). These observations are also consistent with a previous anterograde tracing study in the cat (Ragsdale and Graybiel, 1991). We concluded that neostriatal compartments were differentially innervated by the ML and IL neurons in the rat: 1) The striosome compartment mainly receives thalamic input from Pv, Rh, and Pt neurons (ML); 2) the matrix compartment is heavily innervated by Pf neurons (ILc); and 3) both compartments receive relatively unbiased projections from ILr neurons.

1.4. Functional considerations

The rat ML receives autonomic or visceral information from many subcortical brain regions (Cornwall and Phillipson, 1988; Krout and Loewy, 2000; Krout et al., 2002). The Pv sub-division of the ML is characterized by abundant input from a variety of hypothalamic nuclei (Risold et al., 1997), suggesting that Pv neurons are associated with autonomic or visceral functions. Our findings revealed that thalamostriatal neurons in the ML directed axons to the limbic cortex. In addition, the striosome received afferents from frontal and limbic areas in rats (Gerfen, 1984, 1989; Donoghue and Herkenham, 1986; Kincaid and Wilson, 1996). Therefore, the striosome compartment integrates information from neurons in the limbic cortex and ML with time latency.

Neurons in the striosome project to dopaminergic neurons in the substantia nigra pars compacta (Gerfen, 1985; Jimenez-Castellanos and Graybiel, 1987; Satoda et al., 2002; Fujiyama et al., 2011; Watabe-Uchida et al., 2012; Crittenden et al., 2016). As many researchers suggested (for review, Beste et al., 2018), our findings that the striosome compartment is preferentially innervated by ML neurons suggested that striosome neurons may integrate cognitive/affective information in the cortex and autonomic/visceral information in the hypothalamus. In addition, they may also control the activity of mesencephalic dopamine neurons. A recent study actually revealed that the striosomal neurons can encode the prediction of reward or aversive signals, and send them to dopaminergic neurons (Yoshizawa et al., 2018).

In primates, CM-Pf complex, corresponding to IL in rats, contribute to the thalamostriatal pathway in two ways depending on the predictability of external events *via* the multiple sensory stimuli. One way is monitoring top-down biased control through the cortico-basal ganglia loop system to select signals for action and cognition. The other way is switching from top-down biased control to bottom-up control based on signals of salient external events that are not predictable or are contrary to expectation (for review, Kimura et al., 2004; Smith et al., 2011). Pf-derived thalamostriatal axon terminals, which are located mainly in the matrix compartment (Fig. 3) (Herkenham and Pert, 1981; Sadikot et al., 1990, 1992; Ragsdale and Graybiel, 1991), predominantly synapse asymmetrically on the dendritic shafts of medium-sized spiny projection neurons (MSNs) as well as dendritic shafts of cholinergic and parvalbumin-positive GABAergic interneurons (Xu et al., 1989; Lapper and Bolam, 1992; Smith et al., 1998; Rudkin and Sadikot, 1999; Sidibe and Smith, 1999; Raju et al., 2006; Lacey et al., 2007). The thalamic innervation of striatal cholinergic interneurons conveys significant sensory signals for monitoring and switching of cortico-basal ganglia loop function (Matsumoto et al., 2001; Ding et al., 2010). In contrast, 84% of VGluT2-immunopositive thalamostriatal axon terminals in the striosome form asymmetric axospinous synapses (Fujiyama et al., 2006), suggesting that MSNs are the targets of most ML thalamostriosomal synapses. Axospinous synapses show plasticity (Calabresi et al., 1999, 2000), therefore, it is conceivable that the plasticity of thalamostriosomal synapses, some of which may be formed with Pv axon terminals, permits the integration of cognitive/affective and autonomic/visceral information (see also Ellender et al., 2013).

In conclusion, these findings demonstrate that striosome and matrix compartments are defined by their cortical input, output and various neurochemical markers, and innervation by thalamic neurons. Although these conclusions have previously been made for thalamic nuclei, our single neuron tracing experiments have revealed important information about the individual neuron, including (1) the dendritic morphologies of neurons projecting to specific targets and (2) whether and how single neurons project to multiple targets. Concerning the first point, most ML neurons with type I dendritic morphology and axon fibers preferentially projected to the striosome and limbic cortex. With respect to the second point, our single neuron tracing studies demonstrated that thalamostriatal projections arise from thalamocortical axon collaterals, although subsets of thalamocortical neurons passed through the striatum without forming collaterals (Kuramoto et al., 2009; Clascá et al., 2012; Ohno et al., 2012). In addition, tracing of single neurons revealed that single thalamic neurons favoring striosome or matrix compartments also innervated the cerebral cortical area that innervated the same striatal compartment (Fig. 4). Therefore, the functions of subcompartmental networks in the striatum are influenced by cortical and thalamic afferents presumably with different time latency. This indicates selective dynamics for the striosome and matrix compartments.

Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuint.2019.01.024.

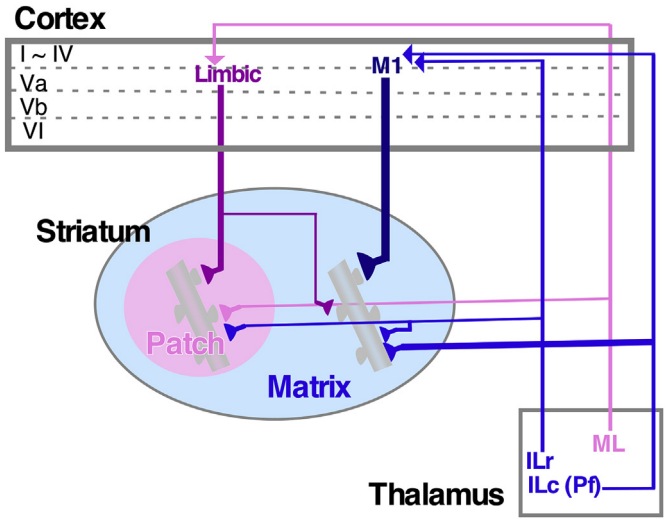

Fig. 4. Summary figure of the present study [from (Unzai et al., 2017) with modifications]. ML thalamostriatal neurons project preferentially to the striosome compartment, whereas Pf thalamostriatal neurons project preferentially to the matrix compartment. ILr thalamostriatal neurons project nonselectively to both compartments. Almost all single thalamostriatal neurons favoring the striosome or matrix compartments also innervated the cerebral cortical area that innervated the same striatal compartment.

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