The Tail of the Striatum: From Anatomy to Connectivity and Function

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Abstract

The dorsal striatum, the largest subcortical structure of the basal ganglia, is critical in controlling motor, procedural and reinforcement-based behaviors. Although in mammals the striatum extends widely along the rostro-caudal axis, current knowledge and derived theories about its anatomo-functional organization largely rely on results obtained from studies of its rostral sectors, leading to potentially oversimplified working models of the striatum as a whole. Recent findings indicate that the extreme caudal part of the striatum, also referred to as the tail of striatum (TS), represents an additional functional domain. Here, we provide an overview of past and recent studies revealing that the TS displays a heterogeneous cell-type-specific organization and a unique input-output connectivity which poises the TS as an integrator of sensory processing.

The forgotten territories of the striatum

The dorsal striatum is the main gateway of the basal ganglia, a group of subcortical nuclei which ensures motor control, action selection, decision making, as well as procedural and reinforcement-based learning [1–3]. In mammals, the striatum is primarily composed of GABAergic striatal projection neurons (SPNs) onto which converge glutamatergic projections from the entire cerebral cortex, thalamus and limbic regions including the hippocampus and amygdala. The multimodal signals conveyed by corticostriatal and thalamostriatal inputs are detected and integrated by SPNs [4]. The computed relevant information is in turn relayed to the output structures of the basal ganglia, thereby allowing the selection and execution of optimized motor sequences [5–8]. These filtering properties are also tightly modulated by monoaminergic signals conveyed by dopaminergic and serotonergic projections originating from the midbrain dopamine (DA) neurons and dorsal raphe nucleus, respectively [9,10].

Despite decades of research, the anatomo-functional organization of the striatum is far from being fully understood. This quest has been largely hampered by the lack of anatomical markers allowing the clear delimitation of territorial boundaries. To date, three major functional domains, dynamically interacting with each other, have been delineated according to the topographic organization of glutamatergic and monoaminergic projections: *i*) the sensorimotor domain comprising the dorsolateral striatum and involved in habit formations, *ii*) the associative domain corresponding to the dorsomedial striatum and important for driving goal-directed behavior, and *iii*) the limbic domain which mediates motivational and affective functions and extend to the ventral striatum [11–15]. Our current understanding of the anatomo-functional organization of striatal circuits has undoubtedly benefited from the delineation of these domains. However, these distinct territories have been defined based on differences spanning across the mediolateral and dorsoventral axes of the rostral striatum. The absence of additional functional domains is somehow surprising since the striatum extends

along the rostro-caudal axis in mammalian brains. Interestingly, recent studies have started providing new insights into the organization of striatal circuits, supporting the existence of at least a fourth striatal functional domain located in the extreme caudal part of the dorsal striatum, also known as the tail of striatum (TS) (**Figure 1**). Here, we summarize key evidence revealing the peculiar anatomo-functional organization of the TS as characterized, among other features, by the non-random spatial distribution of SPNs-expressing dopamine D1 and D2 receptors (D1R-SPNs and D2R-SPNs). We also discuss the high responsiveness of signaling pathways in TS SPNs to psychostimulants. Finally, we review recent findings supporting the role of the TS in guiding appetitive and aversive behaviors relying on the processing of visual and auditory information.

Characterizing the TS by its connectivity

Excitatory afferents

The term "tail of the striatum" (TS) was early attributed to the rat striatal domain receiving cortical projections from the visual cortex [16]. Subsequently, detailed characterization of rodents' cortical afferents projecting to the TS identified the sensorimotor, visual, and auditory cortices as the main sources of TS-projecting neurons [17]. These pioneering observations have been recently confirmed, and further extended, by large-scale projectome studies, whose advanced analyses have precisely redefined the corticostriatal connectivity throughout the rostro-caudal extension of the striatum, including the TS [18–22]. Additional inputs arising from the agranular/granular/dysgranular insular cortices, frontal and temporal association cortices, motor cortex and ecto/peri/entorhinal cortices have been recently described, thus refining the corticostriatal projections map within the TS [18–21] (**Figure 1**). Beyond corticostriatal afferents, inputs from distinct subcortical structures including the amygdala, subiculum, claustrum and endopiriform nucleus also converge into the TS,

suggesting that multisensory processing is likely to occur in the TS [19,20] (**Figure 1**). The degree of convergence into the TS of the aforementioned inputs is however not shared by all mammals. For instance, the caudate tail and posterolateral putamen in cats or macaque monkeys receive almost exclusively excitatory inputs from the visual cortex [23,24]. These observations suggest that the anatomo-functional organization of corticostriatal projections tends to be more segregated throughout the rostro-caudal axis in species in which the dorsal striatum has anatomically demarcated caudate and putamen nuclei.

Although thalamostriatal afferents are evolutionary more ancient than corticostriatal projections, the role of this excitatory network has been for a long time overlooked [25,26]. The analysis of large tracing datasets has recently provided a detailed map of thalamostriatal afferents innervating the rodents' dorsal striatum, including the TS [19,20]. Thus, thalamic nuclei, including the lateral and medial geniculate nuclei, the lateral and ventral posterior nucleus, the parafascicular and posterior intralaminar nuclei, represent the principal sources of thalamic inputs into the TS [19,20,27,28] (**Figure 1**). Interestingly, a similar pattern of connectivity has also been described in the brain of cats, tree shrews and non-human primates [29–32].

Monoaminergic afferents

The functional domains of the striatum receive massive projections from three segregated clusters of DA neurons located in the midbrain [33]. The ones arising from the substantia nigra *pars compacta* (SNc, or A9 group) primarily project to the dorsal striatum, whereas those originating from the retrorubral field (RrF, or A8 group) and the ventral tegmental area (VTA, or A10 group) mainly innervate the ventral striatum [34]. Within these clusters, molecularly-defined SNc and VTA DA neurons displayed biased projections along the rostrocaudal, mediolateral and dorsoventral axes of the DS [33]. Thus, while DA neurons

103 located to the ventral and dorsal tier of the SNc project massively to the lateral and the
104 ventromedial part of the rostral and intermediate DS, respectively, TS-projecting DA neurons
105 arise almost exclusively from the susbtantia nigra *pars lateralis* (SNpl) [33,35–37]. Similarly,
106 DA neurons projecting to the tail of the caudate nucleus (CDt) in cats or monkeys are
107 preferentially located in SNpl, thus revealing that the topographic organization of DA
108 innervation is highly conserved in mammal brains [38,39] (**Figure 1**). Advances in the
109 development of cell-type-specific trans-synaptic tracing methods have allowed to establish a
110 comprehensive cartography of the connectivity of TS-projecting DA neurons [36].
111 Interestingly, unlike DA neurons innervating rostral sectors of the dorsal striatum, TS-
112 projecting DA neurons receive a specific set of monosynaptic inputs from the globus pallidus,
113 zona incerta, parasubthalamic and subthalamic nuclei, entopeduncular nucleus and SNr [36].
114 The peculiarity of TS-projecting DA neurons is also supported by their unique molecular
115 signature characterized by the co-expression of the vesicular glutamate transporter 2
116 (VGLUT2) and the lack of dopamine D2 autoreceptors [33,35,37,40]. These neurochemical
117 features reveal that TS-projecting DA neurons *i*) may co-release DA and glutamate and *ii*)
118 may use other mechanisms than D2R to control the timing and the amount of DA released
119 from presynaptic terminals. Although less characterized, serotonergic (5-HT) innervation
120 from the dorsal raphe nucleus (DRN) has also been described in the TS of rodents as well as
121 in the caudate nucleus of monkeys, thus constituting a second important source of
122 neuromodulation [20,41] (**Figure 1**).
123
124 *TS efferents*
125 TS-output neurons, which consist of SPNs, are segregated into two distinct populations
126 projecting either to the caudal part of the external globus pallidus (GPe) (iSPNs) or to the
127 Ep/GPi and SNr (dSPNs) (**Figure 1**). In the latter, striatal projections arising from the TS are

topographically organized as longitudinal lamina located in the ventral SNr extending from its medial and to its lateral part and comprising the *pars lateralis* [17]. Cell-type-specific tracing tools have been again determinant in defining the circuits controlled by TS SPNs. Thus, TS-output neurons establish monosynaptic contacts with DA neurons located in the SNpl [42] as well as with GABAergic neurons of the lateral SNr [43]. This latter population, which projects to motor thalamic nuclei innervating the M1 and M2 motor cortices, supports the existence of open motor loops that might explain how striatal sub-regions involved in sensory processing modulate and tune motor control outputs [43]. Importantly, anatomical and electrophysiological investigations in the primate CDt have indicated a similar efferent organization for CDt-output dSPNs and iSPNs [44–46], even though a small percentage of traced CDt SPNs (~15%) projected to both caudal SNr and GPe [45].

Delineation of the rodent's TS by its unique cellular architecture

The quest for anatomical markers allowing the delimitation of the TS has only begun. The use of transgenic mice expressing reporters (fluorescent proteins, epitope-tagged proteins, Cre recombinase) driven by specific promoters enables the delimitation of TS domains (**Table 1**). Based on the differential distribution of SPNs expressing either D1R or D2R or both, our group has recently proposed the existence of at least three TS domains: *i*) a D2R/A2aR-SPNs-lacking domain, *ii*) a D1R- and D2R/A2aR-SPNs-intermingled domain and *iii*) a D1R/D2R-SPNs-coexpressing domain [47].

The D2R/A2aR-SPNs-lacking domain

In the course of our attempt of characterizing the spatial distribution of D1R- and D2R-SPNs throughout the rostro-caudal axis of the striatum, we have uncovered in the TS the existence of a longitudinal stripe adjacent to the GPe comprising D1R-expressing SPNs exclusively

153 [35,47]. The absence of D2R/A2aR-SPNs was further supported by the lack of expression of
154 specific markers of this SPN population including D2R, A2aR, enkephalin, Gpr6 and 5'-
155 nucleotidase [48–51]. To date, this represents the best cellular hallmark of this first TS
156 domain which most likely corresponds to the medial part of the TS tri-laminar zone recently
157 described [47,50] (**Figure 2**). The D2R/A2aR-SPNs-lacking domain is also identifiable by a
158 dense plexus of fibers immunoreactive for substance P [35,50], reminiscent of the one
159 described in the "marginal division" (MrD) [52]. However, the lack of μ opioid receptor
160 (MOR) and enkephalin immunoreactivities in D2R/A2aR-SPNs-lacking domain compared to
161 the MrD indicates that they may not be one and the same caudal domain [35,50,52].
162 Local GABA- and ACh-releasing interneurons, which represent ~5% of striatal neurons,
163 play a fundamental role in governing the activity and functions of the striatum [53–55].
164 Beside the peculiar spatial arrangement of D1R-SPNs and D2R-SPNs, a differential
165 distribution of NOS- and ChAT-containing interneurons has been observed in the mouse TS
166 [50]. This cellular feature is of interest, since striatal ChAT interneurons are generally
167 characterized by the co-expression of D2R [56]. In fact, whereas ~94% of ChAT interneurons
168 co-expressed GFP in the dorsal striatum of *Drd2*-eGFP mice, such percentage dropped down
169 to ~17% in the D2R/A2aR-SPNs lacking domain of the TS [35], thereby highlighting a
170 further cellular heterogeneity along the rostro-caudal striatal axis. Importantly, via local cell-
171 to-cell communication, D2R-SPNs and ChAT interneurons are known to modulate the
172 activity of D1R-SPNs [57–62]. Recently, by implementing experimental data with *in silico*
173 modeling, it has been estimated that D2R-SPNs show higher probability to form synaptic
174 contacts with SPNs (both D1R-SPNs and D2R-SPNs) than D1R-SPNs [61,63,64].
175 Interestingly, the virtual absence of D2R-SPNs and the low percentage of ChAT/D2R-
176 positive interneurons in the TS D2R/A2aR-SPNs lacking domain indicate that D1R-SPNs

may possess unique physiological properties (reduced inhibitory drive) that indeed require further mechanistic and functional investigations.

The D1R- and D2R/A2aR-SPNs-intermingled domain

Adjacent to the D2R/A2aR-SPNs-lacking domain, we have identified a D1R- and D2R/A2aR-SPNs-intermingled domain which extends laterally throughout the dorso-ventral axis of the TS [47]. This domain has been further subdivided into two zones corresponding to the intermediate and lateral parts of the tri-laminar zone, respectively [50]. Despite their recent description, up to ten markers can be used to delineate these two zones (**Figure 2, Table 1**). The intermediate zone displays an ovoid shape easily identifiable by the low expression of TH- and DAT-containing fibers [35,47,50]. This zone is also characterized by low levels of D1R and high expression of D2R/A2aR consistent with reduced number of D1R-SPNs compared to D2R/A2aR-SPNs [47,50]. The lateral zone is delineated by an intense enkephalin labeling and a high PKCγ expression [50] (**Figure 2**). Interestingly, corticostriatal sensory projections innervating these two zones are highly segregated. Indeed, the intermediate zone receives excitatory inputs from the auditory cortex, whereas the lateral zone is preferentially innervated by the agranular insular cortex [21]. All these anatomical features, which are highly conserved across the *Muridae* family (mouse, rat, gerbil), suggest that this topographic organization may have functional consequences by compartmentalizing the sensory-related processes integrated and relayed by the TS [47].

D1R/D2R-SPNs-coexpressing domain

The third TS domain lies between the central amygdala (CeA), and the D1R- and D2R/A2aR-SPNs-intermingled domain [47]. This domain is characterized by a proportion of D1R/D2R-coexpressing SPNs (~33%, [47]) much higher than that reported in the dorsal and ventral

202 regions of the rostral striatum, thus constituting one of its main anatomical features
203 [35,47,65–69]. This domain most likely corresponds to the amygdalo-striatal transition area
204 (AST), which processes, together with the adjacent CeA, emotionally relevant information
205 (**Box 1**).
206
207 **Hyper-responsiveness of TS neurons to psychostimulants**
208 Over the past decades, the analysis of DA-evoked molecular signaling events, such as the
209 post-translational modifications (phosphorylation) of ERK, histone H3, and ribosomal protein
210 S6 (rpS6), have been commonly used as molecular readouts for monitoring the activation of
211 SPNs in response to appetitive, aversive and pharmacological stimuli [70]. This approach has
212 provided the first insights into the differential functions of the TS domains.
213 The activation of SPNs in the TS was first described in response to systemic administration
214 of the D1R agonist SKF81297 [71]. Topographic and cell-type-specific analyses indicated
215 that ERK, histone H3, and rpS6 phosphorylations were specifically enhanced in D1R-SPNs
216 located in TS zones processing visual and auditory information [71]. According to the
217 recently proposed delineation of TS territories, the phosphorylation of ERK was restricted to
218 the D2/A2aR-SPNs-lacking domain (medial zone) and the lateral and dorsal parts of the D1R-
219 and D2R/A2aR-SPNs-intermingled domain [47]. Similar patterns of DA-dependent ERK,
220 histone H3 and rpS6 phosphorylation were observed after acute administration of d-
221 amphetamine, methamphetamine, cocaine, methylphenidate, 3,4-
222 methylenedioxymethamphetamine (MDMA) or GBR12783, a selective inhibitor of DA
223 reuptake [47,72] (**Figure 3**). These DA-dependent signaling events, which occurred
224 selectively in D1R-SPNs, depend on the stimulation/activation of D1R [47,72]. Interestingly,
225 ERK activation in the TS appears to be selective for psychostimulants since other classes of
226 drugs, such as hallucinogens (2,5-dimethoxy-4-iodoamphetamine, phencyclidine,

dizocilpine), antidepressants (desipramine, fluoxetine), antipsychotics (haloperidol, raclopride) or mood stabilizers (lithium), failed to trigger ERK activation [47]. Further studies are needed to determine whether this pattern of ERK activation is specific to psychostimulants or shared by other classes of drugs of abuse as it is the case in the shell of the nucleus accumbens and the extended amygdala [73].

Although D1R-mediated ERK, histone H3, and rpS6 phosphorylations require the activation of the cAMP/PKA pathway in both the rostral parts of the dorsal striatum and the TS, recent work indicates that the underlying molecular mechanisms might be different [47,72,74]. Several explanations may account for the potent ERK activation in the D1R-SPNs of the TS D2R/A2aR-SPNs-lacking domain compared to those of the antero-dorsal striatum [47]. Indeed, the absence of the tonic inhibition on ERK phosphorylation mediated by the collateral inhibition of D2R-SPNs onto D1R-SPNs of the medial zone could be one of them. In fact, the D1R-dependent ERK phosphorylation in the antero-dorsal striatum is enhanced in mice lacking D2R in D2R/A2aR-SPNs [75]. Moreover, evidence suggest that the inactivation of the cAMP/PKA signaling normally achieved by PDE1b, PDE10A and PDE4, three SPNs-enriched phosphodiesterases (PDEs) isoforms [76], might not be optimal. Indeed, the lack of PDEs activities in D1R-SPNs of the medial zone certainly account for the rapid and sustained cAMP-dependent phosphorylation of ERK, histone H3 and rpS6 observed in the TS compared to the rostral sectors of the dorsal striatum [35,47,71] (**Figure 3**). Future studies are needed to determine whether D1R-SPNs of the TS D2R/A2aR-SPNs-lacking domain display unique molecular, physiological and functional features (**Figure 3**, **Box 2**).

The TS as an integrator of sensory processing

Although the ability of TS SPNs to respond to a broad range of auditory stimulations has been established for decades [77], only recently the role of the TS in processing auditory

252 information has regained interest. Specifically, recent studies have demonstrated that the
253 acquisition of a sound-driven discrimination task is accompanied by an enhanced auditory
254 corticostriatal plasticity [78,79]. Consequently, inhibition of the auditory corticostriatal
255 excitatory inputs, which tune information for striatum-dependent sound representations,
256 impaired behavioral performance in an auditory frequency discrimination task [27]. It should
257 be noted here that recently identified corticostriatal long-range inhibitory circuits might also
258 contribute to the regulation of auditory processing [80,81]. Similarly, altered responses have
259 been described following the inactivation of thalamostriatal inputs onto TS SPNs, thereby
260 suggesting that both excitatory inputs are necessary to orchestrate auditory decision-making
261 [27]. In addition, inactivation of TS D1R-SPNs impaired sound discrimination and the
262 execution of behavioral tasks requiring auditory decisions [82]. Collectively, these studies
263 support the key role of TS SPNs in integrating auditory sensory information with reward-
264 associated signals to adjust and drive appropriate behavior [83]. A striking observation is that
265 a transient auditory deprivation during development yields to persistent alterations in TS
266 SPNs, thereby suggesting that the acquisition of their auditory-tuning properties might be
267 permanently established during a brief developmental critical period [22]. This latter
268 observation might explain the origin of striatal dysfunctions observed in sensory disorders
269 associated with auditory processing [84,85]. Future studies will be essential in determining
270 whether similar developmental mechanisms regulate the maturation of TS SPNs involved in
271 visual information processing.

272 Reinforcement learning driven by visual and auditory stimuli relies in part on the ability of
273 midbrain DA neurons to encode reward prediction error (RPE), salience and novelty [86–89].
274 Recent work indicates that TS-projecting DA neurons are functionally distinct from DA
275 neurons innervating the dorsal and ventral sectors of the rostral striatum. Photometric Ca^{2+}
276 recordings of DA axons have been determinant in demonstrating that TS-projecting DA

neurons are not only excited in response to novel cues but also by a variety of external sensory stimuli perceived as rewarding, aversive or neutral [90,91]. Their ability to convey general salient signals largely contribute to process reinforcement signals that promote avoidance of threatening stimuli [91]. Further studies are needed to precisely define whether reinforcement learning based on external threats engages distinct TS circuits depending on the nature and the anatomical sources of sensory stimuli (auditory, visual, somatosensory).

Some similarities may exist between the function of TS-projecting DA neurons in rodents and those projecting to the tail of the caudate (CDt) in primates. Indeed, midbrain DA neurons located in the dorsolateral part of the SNc are excited by both rewarding and aversive stimuli [88]. Importantly, these neurons, which also respond to salient visual stimuli, are thought to facilitate long-term memory of reward values of visual objects contributing to automatic and habitual saccades [92]. Importantly, at least two functionally distinct types of DA neurons have been highlighted in the primate SNc: the rostro-medial "update-type DA neurons" which, by mainly projecting to the caudate head (CDh), respond to unpredicted changes, and the CDt-projecting rostro-lateral "sustain-type DA neurons" which encode habitual behaviors [92]. Such functions might support a role of SPNs of the caudate tail in reward-driven visuomotor processing [93–95]. In line with the visual-related functions processed by the primate CDt, lesions of this striatal caudal region elicited an impairment of visual habit formation while sparing visual recognition memory [96]. In addition, neurons of the primate CDt, in opposition to the CDh, have been shown to selectively control automatic saccades-guided behavior when values of visual objects were more stable than flexible, the latter being dependent on the CDh [97]. Recently, taking advantage of optogenetic strategies, a role for CDt D1R-SPNs and D2R-SPNs has emerged as facilitators or suppressors of values-guided saccades, respectively [44,46]. However, whether sensory-related visual and/or auditory

stimuli are processed similarly in the TS/CDt of other species (i.e. human) remain to be fully established.

Concluding remarks

Parsing how the dorsal striatum is functionally organized has been largely hampered by the lack of anatomical markers allowing the clear delimitation of territorial boundaries. Current knowledge on striatal functions and dysfunctions is mainly built upon evidence obtained on rostral sectors of the striatum. However, recent data emerging from large-scale projectome studies have enabled refining the anatomo-functional organization of the dorsal striatum, thus suggesting that the TS may constitute a fourth striatal functional domain. Beyond a unique corticostriatal, thalamostriatal and nigrostriatal connectivity, recent findings indicate that, unlike in most rostral sectors of the dorsal striatum, segregated D1R- and D2R-SPNs are not randomly distributed in the rodents' TS. Future studies are needed to determine whether this key anatomical feature exists in other mammal species, including in non-human and human primate brains.

The existence of anatomically distinct TS domains raises questions about their functions. As mentioned above, the TS participates in encoding visual and auditory stimuli, thus representing a functional hub to allow sensory-associated reward, motor, aversive and decision-making functional outputs. However, how the TS territories and their cell-type components control such functional outputs remains to be established. The recent development of advanced methodologies combining rabies-mediated trans-synaptic tracing and Cre-based cell-type-specific targeting [98] will be valuable to precisely map monosynaptic inputs onto D1R- and D2-SPNs located in the distinct TS domains. Such anatomical characterization will be necessary to understand whether sensory (mainly visual and auditory) information is processed independently by each TS domain. Eventually, single-

cell gene expression profiling will enable defining whether molecular heterogeneity exists amongst TS SPNs that might help to better understand how information is computed in the TS to guide behaviors.

Box 1: The amygdalo-striatal transition area (AST)

Despite its description more than four decades ago, the anatomo-functional organization of the amygdalo-striatal transition area (AST) in rodents and primates remains largely enigmatic [99–102]. Located between the TS and the central nucleus of the amygdala, adjacent to the caudal globus pallidus, the AST receives massive projections from visual and auditory thalamic centers as well as from the insula and amygdala nuclei [100,103–105]. The connectivity and cellular composition of the AST closely resembles those described for the dorsal striatum. Indeed, AST-output neurons segregate and project to the substantia nigra *pars lateralis* and caudoventral globus pallidus [100,106,107]. At the cellular and molecular levels, AST-output neurons comprise D1R-, D2R- and D1R/D2R-SPNs distributed in a random and equal proportion [47]. The AST is characterized by intense calretinin and angiotensin II immunoreactivities, two histological features shared with the extended amygdala [100,105]. Although early studies have suggested a role in the regulation emotional responses [106,108], future studies are required to determine whether salient events are integrated and processed at the level of the AST, and if so, how AST-output neurons contribute to guide motivated behaviors.

Box 2: Molecular and cellular heterogeneity within TS domains

Recent methodological advances in gene expression profiling have unveiled an unexpected molecular heterogeneity among D1R- and D2R-SPNs throughout the dorso-ventral axis of the anterior striatum [56,109,110]. This molecular diversity appears to follow a specific spatial organization as illustrated by recent studies establishing spatio-molecular maps of SPNs in patch, matrix and exopatch compartments [111,112]. Interestingly, emerging evidence points to an additional level of molecular heterogeneity among SPNs throughout the striatal rostro-caudal axis, notably at the level of the TS. Indeed, the absence and/or inefficacy of SPNs-enriched PDEs or phosphatases in D1R-SPNs of the D2R/A2aR-SPNs-lacking TS domain may account for the sustained and enhanced phosphorylation events dependent on cyclic nucleotide signaling [47]. The molecular heterogeneity is not restricted to SPNs since only ~17% of the cholinergic interneurons located in the D2R/A2aR-SPNs-lacking domain express D2R [35]. This observation suggest that the diversity of striatal cholinergic interneurons is not restricted to the dorsoventral axis but also exist throughout the rostro-caudal axis [56,113]. Similar diversity may certainly exist in other striatal interneurons subtypes [114]. Finally, the use of barcoded anatomy resolved by sequencing (BARseq) [115] may provide important insights into the organizing principles underlying the anatomo-functional organization of TS circuits.

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References

1 Hikida, T. *et al.* (2010) Distinct roles of synaptic transmission in direct and indirect striatal pathways to reward and aversive behavior. *Neuron* 66, 896–907

2 Kravitz, A.V. and Kreitzer, A.C. (2012) Striatal mechanisms underlying movement, reinforcement, and punishment. *Physiology (Bethesda)* 27, 167–177

3 Lee, D. *et al.* (2012) Neural basis of reinforcement learning and decision making. *Annu. Rev. Neurosci.* 35, 287–308

4 Wall, N.R. *et al.* (2013) Differential innervation of direct- and indirect-pathway striatal projection neurons. *Neuron* 79, 347–360

5 Peak, J. *et al.* (2019) From learning to action: the integration of dorsal striatal input and output pathways in instrumental conditioning. *Eur. J. Neurosci.* 49, 658–671

6 Hidalgo-Balbuena, A.E. *et al.* (2019) Sensory representations in the striatum provide a temporal reference for learning and executing motor habits. *Nat Commun* 10, 4074

7 Jin, X. and Costa, R.M. (2010) Start/stop signals emerge in nigrostriatal circuits during sequence learning. *Nature* 466, 457–462

8 Jin, X. *et al.* (2014) Basal ganglia subcircuits distinctively encode the parsing and concatenation of action sequences. *Nat. Neurosci.* 17, 423–430

9 Cavaccini, A. *et al.* (2018) Serotonergic Signaling Controls Input-Specific Synaptic Plasticity at Striatal Circuits. *Neuron* 98, 801-816.e7

10 Lerner, T.N. *et al.* (2015) Intact-Brain Analyses Reveal Distinct Information Carried by SNc Dopamine Subcircuits. *Cell* 162, 635–647

11 Balleine, B.W. and O'Doherty, J.P. (2010) Human and rodent homologies in action control: corticostriatal determinants of goal-directed and habitual action. *Neuropsychopharmacology* 35, 48–69

12 Thorn, C.A. *et al.* (2010) Differential dynamics of activity changes in dorsolateral and dorsomedial striatal loops during learning. *Neuron* 66, 781–795

13 Voorn, P. *et al.* (2004) Putting a spin on the dorsal-ventral divide of the striatum. *Trends Neurosci.* 27, 468–474

14 Gremel, C.M. and Costa, R.M. (2013) Orbitofrontal and striatal circuits dynamically encode the shift between goal-directed and habitual actions. *Nat Commun* 4, 2264

15 Floresco, S.B. (2015) The nucleus accumbens: an interface between cognition, emotion, and action. *Annu Rev Psychol* 66, 25–52

16 Donoghue, J.P. and Herkenham, M. (1986) Neostriatal projections from individual cortical fields conform to histochemically distinct striatal compartments in the rat. *Brain Res.* 365, 397–403

17 Deniau, J.M. *et al.* (1996) The lamellar organization of the rat substantia nigra pars reticulata: segregated patterns of striatal afferents and relationship to the topography of

corticostriatal projections. *Neuroscience* 73, 761–781

18 Hintiryan, H. *et al.* (2016) The mouse cortico-striatal projectome. *Nat. Neurosci.* 19, 1100–1114

19 Hunnicutt, B.J. *et al.* (2016) A comprehensive excitatory input map of the striatum reveals novel functional organization. *Elife* 5,

20 Jiang, H. and Kim, H.F. (2018) Anatomical Inputs From the Sensory and Value Structures to the Tail of the Rat Striatum. *Front Neuroanat* 12, 30

21 Miyamoto, Y. *et al.* (2018) Striosome-based map of the mouse striatum that is conformable to both cortical afferent topography and uneven distributions of dopamine D1 and D2 receptor-expressing cells. *Brain Struct Funct* 223, 4275–4291

22 Mowery, T.M. *et al.* (2017) The Sensory Striatum Is Permanently Impaired by Transient Developmental Deprivation. *Cell Rep* 19, 2462–2468

23 Updyke, B.V. (1993) Organization of visual corticostriatal projections in the cat, with observations on visual projections to claustrum and amygdala. *J. Comp. Neurol.* 327, 159–193

24 Seger, C.A. (2013) The visual corticostriatal loop through the tail of the caudate: circuitry and function. *Front Syst Neurosci* 7, 104

25 Smith, Y. *et al.* (2004) The thalamostriatal system: a highly specific network of the basal ganglia circuitry. *Trends Neurosci.* 27, 520–527

26 Reiner, A. *et al.* (2005) Organization and evolution of the avian forebrain. *Anat Rec A Discov Mol Cell Evol Biol* 287, 1080–1102

27 Chen, L. *et al.* (2019) Medial geniculate body and primary auditory cortex differentially contribute to striatal sound representations. *Nat Commun* 10, 418

28 Ponvert, N.D. and Jaramillo, S. (2019) Auditory Thalamostriatal and Corticostriatal Pathways Convey Complementary Information about Sound Features. *J. Neurosci.* 39, 271–280

29 Beckstead, R.M. (1984) A projection to the striatum from the medial subdivision of the posterior group of the thalamus in the cat. *Brain Res.* 300, 351–356

30 Day-Brown, J.D. *et al.* (2010) Pulvinar projections to the striatum and amygdala in the tree shrew. *Front Neuroanat* 4, 143

31 Galvan, A. and Smith, Y. (2011) The primate thalamostriatal systems: Anatomical organization, functional roles and possible involvement in Parkinson's disease. *Basal Ganglia* 1, 179–189

32 Harting, J.K. *et al.* (2001) Striatal projections from the cat visual thalamus. *Eur. J. Neurosci.* 14, 893–896

33 Poulin, J.-F. *et al.* (2020) Classification of Midbrain Dopamine Neurons Using Single-Cell Gene Expression Profiling Approaches. *Trends Neurosci.* 43, 155–169

34 Roeper, J. (2013) Dissecting the diversity of midbrain dopamine neurons. *Trends*

Neurosci. 36, 336–342

35 Gangarossa, G. *et al.* (2013) Spatial distribution of D1R- and D2R-expressing medium-sized spiny neurons differs along the rostro-caudal axis of the mouse dorsal striatum. *Front Neural Circuits* 7, 124

36 Menegas, W. *et al.* (2015) Dopamine neurons projecting to the posterior striatum form an anatomically distinct subclass. *Elife* 4, e10032

37 Poulin, J.-F. *et al.* (2018) Mapping projections of molecularly defined dopamine neuron subtypes using intersectional genetic approaches. *Nat. Neurosci.* 21, 1260–1271

38 Hontanilla, B. *et al.* (1996) A topographic re-evaluation of the nigrostriatal projections to the caudate nucleus in the cat with multiple retrograde tracers. *Neuroscience* 72, 485–503

39 Kim, H.F. *et al.* (2014) Separate groups of dopamine neurons innervate caudate head and tail encoding flexible and stable value memories. *Front Neuroanat* 8, 120

40 Yamaguchi, T. *et al.* (2013) Glutamate neurons in the substantia nigra compacta and retrorubral field. *Eur. J. Neurosci.* 38, 3602–3610

41 Griggs, W.S. *et al.* (2017) Flexible and Stable Value Coding Areas in Caudate Head and Tail Receive Anatomically Distinct Cortical and Subcortical Inputs. *Front. Neuroanat.* 11,

42 Watabe-Uchida, M. *et al.* (2012) Whole-brain mapping of direct inputs to midbrain dopamine neurons. *Neuron* 74, 858–873

43 Aoki, S. *et al.* (2019) An open cortico-basal ganglia loop allows limbic control over motor output via the nigrothalamic pathway. *Elife* 8,

44 Amita, H. *et al.* (2020) Optogenetic manipulation of a value-coding pathway from the primate caudate tail facilitates saccadic gaze shift. *Nat Commun* 11, 1876

45 Amita, H. *et al.* (2019) Neuronal connections of direct and indirect pathways for stable value memory in caudal basal ganglia. *Eur. J. Neurosci.* 49, 712–725

46 Kim, H.F. *et al.* (2017) Indirect Pathway of Caudal Basal Ganglia for Rejection of Valueless Visual Objects. *Neuron* 94, 920-930.e3

47 Gangarossa, G. *et al.* (2019) Contrasting patterns of ERK activation in the tail of the striatum in response to aversive and rewarding signals. *J. Neurochem.* DOI: 10.1111/jnc.14804

48 Harris, J.A. *et al.* (2014) Anatomical characterization of Cre driver mice for neural circuit mapping and manipulation. *Front Neural Circuits* 8, 76

49 Koshimizu, Y. *et al.* (2008) Paucity of enkephalin production in neostriatal striosomal neurons: analysis with preproenkephalin-green fluorescent protein transgenic mice. *Eur. J. Neurosci.* 28, 2053–2064

50 Miyamoto, Y. *et al.* (2019) Three divisions of the mouse caudal striatum differ in the proportions of dopamine D1 and D2 receptor-expressing cells, distribution of dopaminergic axons, and composition of cholinergic and GABAergic interneurons. *Brain Struct Funct* 224,

2703–2716

51 Schoen, S.W. and Graybiel, A.M. (1993) Species-specific patterns of glycoprotein expression in the developing rodent caudoputamen: association of 5'-nucleotidase activity with dopamine islands and striosomes in rat, but with extrastriosomal matrix in mouse. *J. Comp. Neurol.* 333, 578–596

52 Shu, S.Y. *et al.* (2003) New component of the limbic system: Marginal division of the neostriatum that links the limbic system to the basal nucleus of Meynert. *J. Neurosci. Res.* 71, 751–757

53 Fino, E. *et al.* (2018) Region-specific and state-dependent action of striatal GABAergic interneurons. *Nat Commun* 9, 3339

54 Gritton, H.J. *et al.* (2019) Unique contributions of parvalbumin and cholinergic interneurons in organizing striatal networks during movement. *Nat. Neurosci.* 22, 586–597

55 Zucca, S. *et al.* (2018) Pauses in cholinergic interneuron firing exert an inhibitory control on striatal output in vivo. *Elife* 7,

56 Puighermanal, E. *et al.* (2020) Functional and molecular heterogeneity of D2R neurons along dorsal ventral axis in the striatum. *Nat Commun* 11, 1957

57 Czubayko, U. and Plenz, D. (2002) Fast synaptic transmission between striatal spiny projection neurons. *Proc. Natl. Acad. Sci. U.S.A.* 99, 15764–15769

58 English, D.F. *et al.* (2011) GABAergic circuits mediate the reinforcement-related signals of striatal cholinergic interneurons. *Nat. Neurosci.* 15, 123–130

59 Koos, T. *et al.* (2004) Comparison of IPSCs evoked by spiny and fast-spiking neurons in the neostriatum. *J. Neurosci.* 24, 7916–7922

60 Oldenburg, I.A. and Ding, J.B. (2011) Cholinergic modulation of synaptic integration and dendritic excitability in the striatum. *Curr. Opin. Neurobiol.* 21, 425–432

61 Taverna, S. *et al.* (2008) Recurrent collateral connections of striatal medium spiny neurons are disrupted in models of Parkinson's disease. *J. Neurosci.* 28, 5504–5512

62 Witten, I.B. *et al.* (2010) Cholinergic interneurons control local circuit activity and cocaine conditioning. *Science* 330, 1677–1681

63 Hjorth, J.J.J. *et al.* (2020) The microcircuits of striatum in silico. *Proc. Natl. Acad. Sci. U.S.A.* 117, 9554–9565

64 Planert, H. *et al.* (2010) Dynamics of synaptic transmission between fast-spiking interneurons and striatal projection neurons of the direct and indirect pathways. *J. Neurosci.* 30, 3499–3507

65 Gangarossa, G. *et al.* (2013) Distribution and compartmental organization of GABAergic medium-sized spiny neurons in the mouse nucleus accumbens. *Front Neural Circuits* 7, 22

66 Gagnon, D. *et al.* (2017) Striatal Neurons Expressing D1 and D2 Receptors are Morphologically Distinct and Differently Affected by Dopamine Denervation in Mice. *Sci*

Rep 7, 41432

67 Wei, X. *et al.* (2018) Dopamine D1 or D2 receptor-expressing neurons in the central nervous system. *Addict Biol* 23, 569–584

68 Frederick, A.L. *et al.* (2015) Evidence against dopamine D1/D2 receptor heteromers. *Mol. Psychiatry* 20, 1373–1385

69 Rico, A.J. *et al.* (2017) Neurochemical evidence supporting dopamine D1–D2 receptor heteromers in the striatum of the long-tailed macaque: changes following dopaminergic manipulation. *Brain Struct Funct* 222, 1767–1784

70 Valjent, E. *et al.* (2019) Dopamine signaling in the striatum. In *Advances in Protein Chemistry and Structural Biology* Academic Press

71 Gangarossa, G. *et al.* (2013) Combinatorial topography and cell-type specific regulation of the ERK pathway by dopaminergic agonists in the mouse striatum. *Brain Struct Funct* 218, 405–419

72 Biever, A. *et al.* (2015) PKA-dependent phosphorylation of ribosomal protein S6 does not correlate with translation efficiency in striatonigral and striatopallidal medium-sized spiny neurons. *J. Neurosci.* 35, 4113–4130

73 Valjent, E. *et al.* (2004) Addictive and non-addictive drugs induce distinct and specific patterns of ERK activation in mouse brain. *Eur. J. Neurosci.* 19, 1826–1836

74 Polito, M. *et al.* (2015) Selective Effects of PDE10A Inhibitors on Striatopallidal Neurons Require Phosphatase Inhibition by DARPP-32. *eNeuro* 2,

75 Dobbs, L.K. *et al.* (2019) D1 receptor hypersensitivity in mice with low striatal D2 receptors facilitates select cocaine behaviors. *Neuropsychopharmacology* 44, 805–816

76 Nishi, A. *et al.* (2008) Distinct roles of PDE4 and PDE10A in the regulation of cAMP/PKA signaling in the striatum. *J. Neurosci.* 28, 10460–10471

77 Bordi, F. and LeDoux, J. (1992) Sensory tuning beyond the sensory system: an initial analysis of auditory response properties of neurons in the lateral amygdaloid nucleus and overlying areas of the striatum. *J. Neurosci.* 12, 2493–2503

78 Znamenskiy, P. and Zador, A.M. (2013) Corticostriatal neurons in auditory cortex drive decisions during auditory discrimination. *Nature* 497, 482–485

79 Xiong, Q. *et al.* (2015) Selective corticostriatal plasticity during acquisition of an auditory discrimination task. *Nature* 521, 348–351

80 Rock, C. *et al.* (2016) An inhibitory corticostriatal pathway. *Elife* 5,

81 Bertero, A. *et al.* (2020) Auditory Long-Range Parvalbumin Cortico-Striatal Neurons. *Front Neural Circuits* 14, 45

82 Guo, L. *et al.* (2018) Stable representation of sounds in the posterior striatum during flexible auditory decisions. *Nat Commun* 9, 1534

83 Guo, L. *et al.* (2019) Choice-Selective Neurons in the Auditory Cortex and in Its

557 Striatal Target Encode Reward Expectation. *J. Neurosci.* 39, 3687–3697

558 84 Shepherd, G.M.G. (2013) Corticostriatal connectivity and its role in disease. *Nat. Rev.*
559 *Neurosci.* 14, 278–291

560 85 Lim, S.-J. *et al.* (2019) Role of the striatum in incidental learning of sound categories.
561 *Proc. Natl. Acad. Sci. U.S.A.* 116, 4671–4680

562 86 Cohen, J.Y. *et al.* (2012) Neuron-type-specific signals for reward and punishment in
563 the ventral tegmental area. *Nature* 482, 85–88

564 87 Glimcher, P.W. (2011) Understanding dopamine and reinforcement learning: the
565 dopamine reward prediction error hypothesis. *Proc. Natl. Acad. Sci. U.S.A.* 108 Suppl 3,
566 15647–15654

567 88 Matsumoto, M. and Hikosaka, O. (2009) Two types of dopamine neuron distinctly
568 convey positive and negative motivational signals. *Nature* 459, 837–841

569 89 Morrens, J. *et al.* (2020) Cue-Evoked Dopamine Promotes Conditioned Responding
570 during Learning. *Neuron* 106, 142-153.e7

571 90 Menegas, W. *et al.* (2017) Opposite initialization to novel cues in dopamine signaling
572 in ventral and posterior striatum in mice. *Elife* 6,

573 91 Menegas, W. *et al.* (2018) Dopamine neurons projecting to the posterior striatum
574 reinforce avoidance of threatening stimuli. *Nat. Neurosci.* 21, 1421–1430

575 92 Kim, H.F. *et al.* (2015) Dopamine Neurons Encoding Long-Term Memory of Object
576 Value for Habitual Behavior. *Cell* 163, 1165–1175

577 93 Yamamoto, S. *et al.* (2012) What and where information in the caudate tail guides
578 saccades to visual objects. *J. Neurosci.* 32, 11005–11016

579 94 Yamamoto, S. *et al.* (2013) Reward value-contingent changes of visual responses in
580 the primate caudate tail associated with a visuomotor skill. *J. Neurosci.* 33, 11227–11238

581 95 Hikosaka, O. *et al.* (2014) Basal ganglia circuits for reward value-guided behavior.
582 *Annu. Rev. Neurosci.* 37, 289–306

583 96 Fernandez-Ruiz, J. *et al.* (2001) Visual habit formation in monkeys with neurotoxic
584 lesions of the ventrocaudal neostriatum. *Proc. Natl. Acad. Sci. U.S.A.* 98, 4196–4201

585 97 Kim, H.F. and Hikosaka, O. (2013) Distinct basal ganglia circuits controlling
586 behaviors guided by flexible and stable values. *Neuron* 79, 1001–1010

587 98 Sjulson, L. *et al.* (2016) Cell-Specific Targeting of Genetically Encoded Tools for
588 Neuroscience. *Annu. Rev. Genet.* 50, 571–594

589 99 Alheid, G.F. *et al.* (1998) The neuronal organization of the supracapsular part of the
590 stria terminalis in the rat: the dorsal component of the extended amygdala. *Neuroscience* 84,
591 967–996

592 100 Shammah-Lagnado, S.J. *et al.* (1999) Afferent connections of the interstitial nucleus
593 of the posterior limb of the anterior commissure and adjacent amygdalostriatal transition area

in the rat. *Neuroscience* 94, 1097–1123

101 Cho, Y.T. *et al.* (2013) Cortico-amygdala-striatal circuits are organized as hierarchical subsystems through the primate amygdala. *J. Neurosci.* 33, 14017–14030

102 Fudge, J.L. and Tucker, T. (2009) Amygdala projections to central amygdaloid nucleus subdivisions and transition zones in the primate. *Neuroscience* 159, 819–841

103 Turner, B.H. and Herkenham, M. (1991) Thalamoamygdaloid projections in the rat: a test of the amygdala's role in sensory processing. *J. Comp. Neurol.* 313, 295–325

104 Doron, N.N. and Ledoux, J.E. (1999) Organization of projections to the lateral amygdala from auditory and visual areas of the thalamus in the rat. *J. Comp. Neurol.* 412, 383–409

105 Jolkkonen, E. *et al.* (2001) Interconnectivity between the amygdaloid complex and the amygdalostriatal transition area: a PHA-L study in rat. *J. Comp. Neurol.* 431, 39–58

106 LeDoux, J.E. *et al.* (1990) The lateral amygdaloid nucleus: sensory interface of the amygdala in fear conditioning. *J. Neurosci.* 10, 1062–1069

107 Shammah-Lagnado, S.J. *et al.* (1996) Efferent connections of the caudal part of the globus pallidus in the rat. *J. Comp. Neurol.* 376, 489–507

108 Trogrlic, L. *et al.* (2011) Context fear learning specifically activates distinct populations of neurons in amygdala and hypothalamus. *Learn. Mem.* 18, 678–687

109 Gokce, O. *et al.* (2016) Cellular Taxonomy of the Mouse Striatum as Revealed by Single-Cell RNA-Seq. *Cell Rep* 16, 1126–1137

110 Saunders, A. *et al.* (2018) Molecular Diversity and Specializations among the Cells of the Adult Mouse Brain. *Cell* 174, 1015-1030.e16

111 Märtin, A. *et al.* (2019) A Spatiomolecular Map of the Striatum. *Cell Rep* 29, 4320-4333.e5

112 Stanley, G. *et al.* (2020) Continuous and Discrete Neuron Types of the Adult Murine Striatum. *Neuron* 105, 688-699.e8

113 Virk, M.S. *et al.* (2016) Opposing roles for serotonin in cholinergic neurons of the ventral and dorsal striatum. *Proc. Natl. Acad. Sci. U.S.A.* 113, 734–739

114 Muñoz-Manchado, A.B. *et al.* (2018) Diversity of Interneurons in the Dorsal Striatum Revealed by Single-Cell RNA Sequencing and PatchSeq. *Cell Rep* 24, 2179-2190.e7

115 Chen, X. *et al.* (2019) High-Throughput Mapping of Long-Range Neuronal Projection Using In Situ Sequencing. *Cell* 179, 772-786.e19

116 Franklin, K. and Paxinos, G., K. The Mouse Brain in Stereotaxic Coordinates, 3rd Edn. . (2008), Elsevier

117 Gong, S. *et al.* (2003) A gene expression atlas of the central nervous system based on bacterial artificial chromosomes. *Nature* 425, 917–925

631

632 **Figure legends**

633 **Figure 1: Delineating the tail of the striatum.**

634 (**a**) Coronal view of the tail of the striatum (TS) across different species. In rodents, the TS
635 consists of one entity, whereas in tree shrews, cats and non-human primates the TS consists of
636 the tail of the caudate nucleus (CDt) and the posterolateral putamen. (**b**) Schematic of rodents'
637 TS inputs. The TS receives excitatory afferents (in violet) from a broad range of cortical areas
638 throughout its rostro-caudal extension (from bregma -1.22 mm to -0.94 mm). This includes
639 the frontal association cortex (FrA), motor cortex (M1/2), somatosensory cortex (S1/2),
640 agranular, granular, dysgranular insular cortex (AI/GI/DI), visual cortex (Vis), auditory cortex
641 (Aud), ecto-/peri-/entorhinal cortex (Rhi) and temporal association cortex (Tem). The TS also
642 integrates thalamic inputs arising from the lateral and ventral posterior nuclei (LP and
643 VPM/VPL), medial and lateral geniculate nuclei (MG and LG), mediodorsal nucleus (MD),
644 parafascicular nucleus (PF), posterior intralaminar nucleus (PIL) and pulvinar nucleus. The
645 two main sources of monoaminergic regulation comprise dopaminergic (DA) neurons (in
646 orange) arising from the substantia nigra *pars lateralis* (SNpl) and serotonergic (5-HT) (in
647 turquoise) innervation from the dorsal raphe nucleus (DRN). (**c**) Schematic of rodents' TS
648 efferents. TS-output neurons are GABAergic SPNs that segregate into two distinct
649 populations projecting either to the caudal part of the external globus pallidus (GPe) (D2R-
650 SPNs or iSPNs) or to the Ep/GPi and SNpr (D1R-SPNs or dSPNs). Schemes have been
651 adapted from the mouse brain atlas [116].

652

653 **Figure 2: Identification of distinct domains of the rodent TS.**

654 (**a**) Schematic cartoon illustrating the TS. Double immunofluorescence of D2R (yellow) and
655 GFP (cyan) in the TS of *Drd2*-eGFP mice. D2R (cyan) immunolabeling in the rat and gerbil

TS. Note the presence in all these species of a longitudinal stripe adjacent to the GPe lacking D2R-expressing SPNs. Scale bar, 200 µm. (**b**) Cartoons and list of known markers allowing the delineation of the D2R/A2aR-SPNs-lacking domain (in violet), and the two zones of the D1R- and D2R/A2aR-SPNs-intermingled domain corresponding to the intermediate (in orange) and lateral (in dark grey) parts of the tri-laminar zone [50]. Cx: Cortex; cc: corpus callosum; GPe: external globus pallidus; AST: amygdalostriatal transition; CeA: central amygdala, BLA: basolateral amygdala, LA: lateral amygdala; TS: tail of the striatum. Schemes have been adapted from the mouse brain atlas [116].

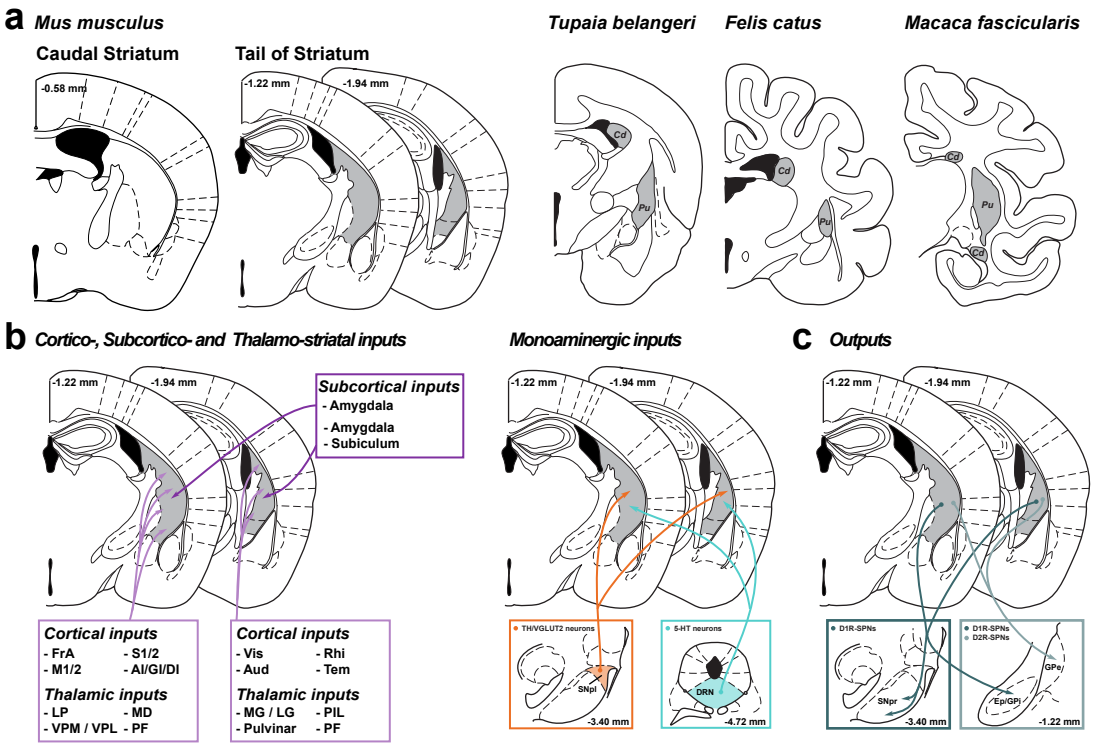
Figure 3: Distinct patterns of ERK phosphorylation within the mouse's TS domains.

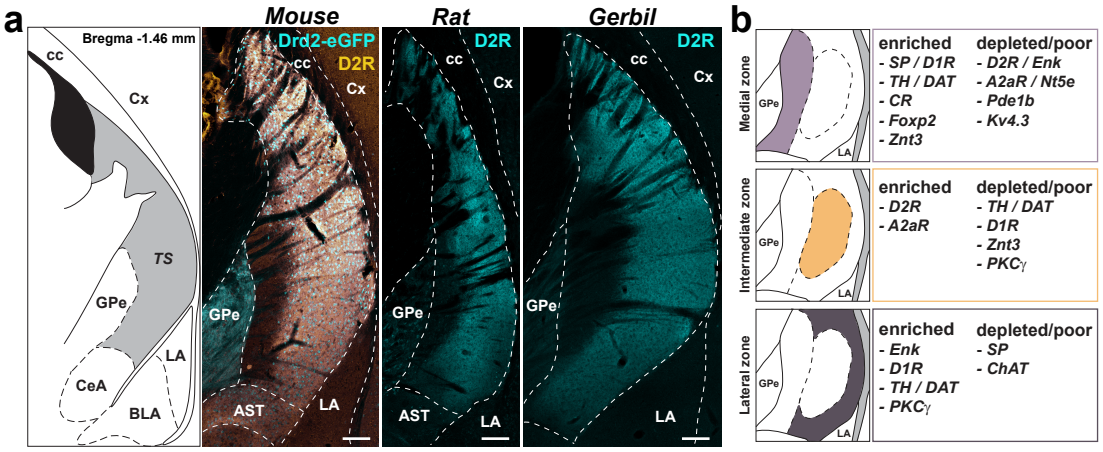
(**a**) Double immunofluorescence of pERK (yellow) and TH (cyan) in the TS of C57BL/6 mice 15 min after d-amphetamine (10 mg/kg) administration. Note that d-amphetamine-induced ERK phosphorylation occurs preferentially in the D1R-SPNs of the D2R/A2aR-SPNs-lacking domain. Scale bar, 200 µm. High magnification of the area delineated by the white dashed rectangle. Scale bar, 100 µm. (**b**) Cartoons summarizing the distinct patterns of ERK phosphorylation induced by a single injection of d-amphetamine (d-amph), MDMA, cocaine, GBR12783 (DAT reuptake inhibitor), methylphenidate and PDE10A inhibitor (papaverine) in the distinct mouse' TS domains. Note that papaverine increases preferentially pERK in D2R-SPNs of the intermediate part of the D1R- and D2R/A2aR-SPNs-intermingled domain. Cx: Cortex; cc: corpus callosum; GPe: external globus pallidus; AST: amygdalostriatal transition; LA: lateral amygdala; TS: tail of the striatum. Schemes have been adapted from the mouse brain atlas [116].

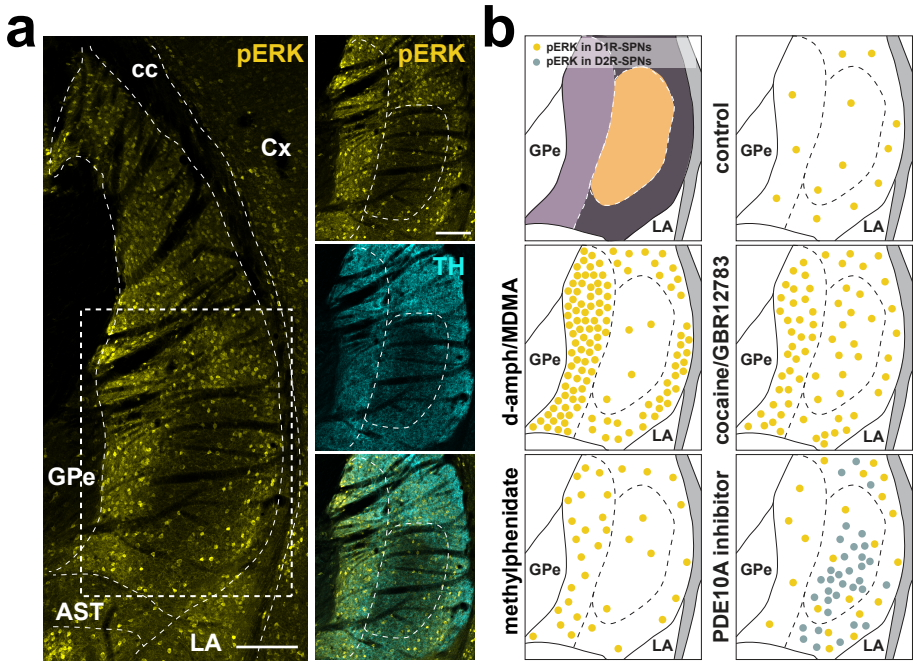
Table 1. Markers with distinct expression in the medial, intermediate and lateral zones of the TS

Markers	Zones/Domains	Species	References
SP	medial-enriched	Mouse	[21,35,50]
D1R	intermediate-poor	Mouse, Rat	[35,47]
		Drd1a-eGFP mice	[35]
		Drd1a-tdTomato mice	[47]
TH	intermediate-poor	Mouse, Rat	[47,50]
	medial-enriched	*Th-Cre:tdTomato* mice	[48](Allen Brain Atlas)
CR	medial-enriched	Mouse, rat	[47,50]
D2R	medial-poor	Mouse, Rat, Gerbil	[47]
		Drd2-eGFP, *Drd2-Cre:RCE* mice	[35]
		Drd2-Cre:RCE or LacZ-TauGFP mice	
A2aR	medial-poor	Mouse, Rat, Gerbil	[47]
		Adora2a-Cre:YFP mice	[35]
PDE1b	medial-poor	*Pde1b-Cre* mice	[117](Gensat)
Enk	medial-poor	Mouse	[47,50]
		Penk-2A-CreERT2:tdTomato mice	[48](Allen Brain Atlas)
		PPE-eGFP mice	[49]
NT5E	medial-poor	Rat	[51]

SP: Substance P; D1R: Dopamine D1 receptor; TH: Tyrosine hydroxylase; CR: Calretinin; D2R: Dopamine D2 receptor; A2aR: Adenosine A2a receptor; PDE1b; Phosphodiesterase 1b: Enk; Enkephalin: NT5E; Ecto-5'-nucleotidase


a
Mus musculus
Caudal Striatum
Tail of Striatum
-0.58 mm
-1.22 mm
-1.94 mm
Tupaia belangeri
Felis catus
Macaca fascicularis
Cd
Pu
b
Cortico-, Subcortico- and Thalamo-striatal inputs
Subcortical inputs
- Amygdala
- Amygdala
- Subiculum
Cortical inputs
- FrA
- S1/2
- M1/2
- AI/GI/DI
Thalamic inputs
- LP
- MD
- VPM / VPL
- PF
Cortical inputs
- Vis
- Rhi
- Aud
- Tem
Thalamic inputs
- MG / LG
- PIL
- Pulvinar
- PF
Monoaminergic inputs
TH/VGLUT2 neurons
5-HT neurons
SNpl
DRN
-3.40 mm
-4.72 mm
c
Outputs
D1R-SPNs
D2R-SPNs
SNpr
GPe/
Ep/GPi
-3.40 mm
-1.22 mm


a
Mouse
Rat
Gerbil
Bregma -1.46 mm
cc
Cx
TS
GPe
LA
CeA
BLA
Drd2-eGFP
D2R
AST
b
Medial zone
Intermediate zone
Lateral zone
enriched
depleted/poor
- SP / D1R
- TH / DAT
- CR
- Foxp2
- Znt3
- D2R / Enk
- A2aR / Nt5e
- Pde1b
- Kv4.3
- D2R
- A2aR
- TH / DAT
- D1R
- Znt3
- PKCγ
- Enk
- D1R
- TH / DAT
- PKCγ
- SP
- ChAT


a
pERK
cc
Cx
GPe
AST
LA
pERK
TH
b
pERK in D1R-SPNs
pERK in D2R-SPNs
GPe
LA
control
d-amph/MDMA
cocaine/GBR12783
methylphenidate
PDE10A inhibitor