



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

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## 1 The Tail of the Striatum: from anatomy to connectivity and function

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16 psychostimulants; striatal projection neurons

17    **Abstract**

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

28    **The forgotten territories of the striatum**

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

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

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

63

#### 64 **Characterizing the TS by its connectivity**

##### 65 *Excitatory afferents*

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

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

85 Although thalamostriatal afferents are evolutionary more ancient than corticostriatal  
86 projections, the role of this excitatory network has been for a long time overlooked [25,26].  
87 The analysis of large tracing datasets has recently provided a detailed map of thalamostriatal  
88 afferents innervating the rodents' dorsal striatum, including the TS [19,20]. Thus, thalamic  
89 nuclei, including the lateral and medial geniculate nuclei, the lateral and ventral posterior  
90 nucleus, the parafascicular and posterior intralaminar nuclei, represent the principal sources of  
91 thalamic inputs into the TS [19,20,27,28] (**Figure 1**). Interestingly, a similar pattern of  
92 connectivity has also been described in the brain of cats, tree shrews and non-human primates  
93 [29–32].

94

#### 95 *Monoaminergic afferents*

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

located to the ventral and dorsal tier of the SNc project massively to the lateral and the ventromedial part of the rostral and intermediate DS, respectively, TS-projecting DA neurons arise almost exclusively from the substantia nigra *pars lateralis* (SNpl) [33,35–37]. Similarly, DA neurons projecting to the tail of the caudate nucleus (CDt) in cats or monkeys are preferentially located in SNpl, thus revealing that the topographic organization of DA innervation is highly conserved in mammal brains [38,39] (**Figure 1**). Advances in the development of cell-type-specific trans-synaptic tracing methods have allowed to establish a comprehensive cartography of the connectivity of TS-projecting DA neurons [36]. Interestingly, unlike DA neurons innervating rostral sectors of the dorsal striatum, TS-projecting DA neurons receive a specific set of monosynaptic inputs from the globus pallidus, zona incerta, parasubthalamic and subthalamic nuclei, entopeduncular nucleus and SNr [36]. The peculiarity of TS-projecting DA neurons is also supported by their unique molecular signature characterized by the co-expression of the vesicular glutamate transporter 2 (VGLUT2) and the lack of dopamine D2 autoreceptors [33,35,37,40]. These neurochemical features reveal that TS-projecting DA neurons *i*) may co-release DA and glutamate and *ii*) may use other mechanisms than D2R to control the timing and the amount of DA released from presynaptic terminals. Although less characterized, serotonergic (5-HT) innervation from the dorsal raphe nucleus (DRN) has also been described in the TS of rodents as well as in the caudate nucleus of monkeys, thus constituting a second important source of 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

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

139

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

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

148

#### 149 *The D2R/A2aR-SPNs-lacking domain*

150 In the course of our attempt of characterizing the spatial distribution of D1R- and D2R-SPNs  
151 throughout the rostro-caudal axis of the striatum, we have uncovered in the TS the existence  
152 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  $\mu$  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

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

179

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

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

197

198 *D1R/D2R-SPNs-coexpressing domain*

199 The third TS domain lies between the central amygdala (CeA), and the D1R- and D2R/A2aR-  
200 SPNs-intermingled domain [47]. This domain is characterized by a proportion of D1R/D2R-  
201 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 GBR12983, 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,

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

232 Although D1R-mediated ERK, histone H3, and rpS6 phosphorylations require the  
233 activation of the cAMP/PKA pathway in both the rostral parts of the dorsal striatum and the  
234 TS, recent work indicates that the underlying molecular mechanisms might be different  
235 [47,72,74]. Several explanations may account for the potent ERK activation in the D1R-SPNs  
236 of the TS D2R/A2aR-SPNs-lacking domain compared to those of the antero-dorsal striatum  
237 [47]. Indeed, the absence of the tonic inhibition on ERK phosphorylation mediated by the  
238 collateral inhibition of D2R-SPNs onto D1R-SPNs of the medial zone could be one of them.  
239 In fact, the D1R-dependent ERK phosphorylation in the antero-dorsal striatum is enhanced in  
240 mice lacking D2R in D2R/A2aR-SPNs [75]. Moreover, evidence suggest that the inactivation  
241 of the cAMP/PKA signaling normally achieved by PDE1b, PDE10A and PDE4, three SPNs-  
242 enriched phosphodiesterases (PDEs) isoforms [76], might not be optimal. Indeed, the lack of  
243 PDEs activities in D1R-SPNs of the medial zone certainly account for the rapid and sustained  
244 cAMP-dependent phosphorylation of ERK, histone H3 and rpS6 observed in the TS compared  
245 to the rostral sectors of the dorsal striatum [35,47,71] (**Figure 3**). Future studies are needed to  
246 determine whether D1R-SPNs of the TS D2R/A2aR-SPNs-lacking domain display unique  
247 molecular, physiological and functional features (**Figure 3, Box 2**).

248

#### 249 **The TS as an integrator of sensory processing**

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

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

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

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

283 Some similarities may exist between the function of TS-projecting DA neurons in rodents  
284 and those projecting to the tail of the caudate (CDt) in primates. Indeed, midbrain DA neurons  
285 located in the dorsolateral part of the SNC are excited by both rewarding and aversive stimuli  
286 [88]. Importantly, these neurons, which also respond to salient visual stimuli, are thought to  
287 facilitate long-term memory of reward values of visual objects contributing to automatic and  
288 habitual saccades [92]. Importantly, at least two functionally distinct types of DA neurons  
289 have been highlighted in the primate SNC: the rostro-medial “update-type DA neurons”  
290 which, by mainly projecting to the caudate head (CDh), respond to unpredicted changes, and  
291 the CDt-projecting rostro-lateral “sustain-type DA neurons” which encode habitual behaviors  
292 [92]. Such functions might support a role of SPNs of the caudate tail in reward-driven  
293 visuomotor processing [93–95]. In line with the visual-related functions processed by the  
294 primate CDt, lesions of this striatal caudal region elicited an impairment of visual habit  
295 formation while sparing visual recognition memory [96]. In addition, neurons of the primate  
296 CDt, in opposition to the CDh, have been shown to selectively control automatic saccades-  
297 guided behavior when values of visual objects were more stable than flexible, the latter being  
298 dependent on the CDh [97]. Recently, taking advantage of optogenetic strategies, a role for  
299 CDt D1R-SPNs and D2R-SPNs has emerged as facilitators or suppressors of values-guided  
300 saccades, respectively [44,46]. However, whether sensory-related visual and/or auditory

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

303

304 **Concluding remarks**

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

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

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

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

330 Despite its description more than four decades ago, the anatomo-functional organization of  
331 the amygdalo-striatal transition area (AST) in rodents and primates remains largely enigmatic  
332 [99–102]. Located between the TS and the central nucleus of the amygdala, adjacent to the  
333 caudal globus pallidus, the AST receives massive projections from visual and auditory  
334 thalamic centers as well as from the insula and amygdala nuclei [100,103–105]. The  
335 connectivity and cellular composition of the AST closely resembles those described for the  
336 dorsal striatum. Indeed, AST-output neurons segregate and project to the substantia nigra *pars*  
337 *lateralis* and caudoventral globus pallidus [100,106,107]. At the cellular and molecular levels,  
338 AST-output neurons comprise D1R-, D2R- and D1R/D2R-SPNs distributed in a random and  
339 equal proportion [47]. The AST is characterized by intense calretinin and angiotensin II  
340 immunoreactivities, two histological features shared with the extended amygdala [100,105].  
341 Although early studies have suggested a role in the regulation emotional responses [106,108],  
342 future studies are required to determine whether salient events are integrated and processed at  
343 the level of the AST, and if so, how AST-output neurons contribute to guide motivated  
344 behaviors.

345 **Box 2: Molecular and cellular heterogeneity within TS domains**

346 Recent methodological advances in gene expression profiling have unveiled an unexpected  
347 molecular heterogeneity among D1R- and D2R-SPNs throughout the dorso-ventral axis of the  
348 anterior striatum [56,109,110]. This molecular diversity appears to follow a specific spatial  
349 organization as illustrated by recent studies establishing spatio-molecular maps of SPNs in  
350 patch, matrix and exopatch compartments [111,112]. Interestingly, emerging evidence points  
351 to an additional level of molecular heterogeneity among SPNs throughout the striatal rostro-  
352 caudal axis, notably at the level of the TS. Indeed, the absence and/or inefficacy of SPNs-  
353 enriched PDEs or phosphatases in D1R-SPNs of the D2R/A2aR-SPNs-lacking TS domain  
354 may account for the sustained and enhanced phosphorylation events dependent on cyclic  
355 nucleotide signaling [47]. The molecular heterogeneity is not restricted to SPNs since only  
356 ~17% of the cholinergic interneurons located in the D2R/A2aR-SPNs-lacking domain express  
357 D2R [35]. This observation suggest that the diversity of striatal cholinergic interneurons is not  
358 restricted to the dorsoventral axis but also exist throughout the rostro-caudal axis [56,113].  
359 Similar diversity may certainly exist in other striatal interneurons subtypes [114]. Finally, the  
360 use of barcoded anatomy resolved by sequencing (BARseq) [115] may provide important  
361 insights into the organizing principles underlying the anatomo-functional organization of TS  
362 circuits.

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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

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

664

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

666 (a) Double immunofluorescence of pERK (yellow) and TH (cyan) in the TS of C57BL/6 mice  
667 15 min after d-amphetamine (10 mg/kg) administration. Note that d-amphetamine-induced  
668 ERK phosphorylation occurs preferentially in the D1R-SPNs of the D2R/A2aR-SPNs-lacking  
669 domain. Scale bar, 200  $\mu$ m. High magnification of the area delineated by the white dashed  
670 rectangle. Scale bar, 100  $\mu$ m. (b) Cartoons summarizing the distinct patterns of ERK  
671 phosphorylation induced by a single injection of d-amphetamine (d-amph), MDMA, cocaine,  
672 GBR12783 (DAT reuptake inhibitor), methylphenidate and PDE10A inhibitor (papaverine) in  
673 the distinct mouse' TS domains. Note that papaverine increases preferentially pERK in D2R-  
674 SPNs of the intermediate part of the D1R- and D2R/A2aR-SPNs-intermingled domain. Cx:  
675 Cortex; cc: corpus callosum; GPe: external globus pallidus; AST: amygdalostriatal transition;  
676 LA: lateral amygdala; TS: tail of the striatum. Schemes have been adapted from the mouse  
677 brain atlas [116].

678

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

680	681 <b>Markers</b>	682 <b>Zones/Domains</b>	683 <b>Species</b>	684 <b>References</b>
685	686 SP	687 medial-enriched	688 Mouse	689 [21,35,50]
690	691 D1R	692 intermediate-poor	693 Mouse, Rat	694 [35,47]
695	696	697	698 <i>Drd1a-eGFP</i> mice	699 [35]
700	701	702 CR	703 <i>Drd1a-tdTomato</i> mice	704 [47]
705	706 D2R	707 medial-enriched	708 Mouse, Rat	709 [47,50]
710	711 TH	712 medial-enriched	713 <i>Th-Cre:tdTomato</i> mice	714 [48](Allen Brain Atlas)
715	716 CR	717 medial-poor	718 Mouse, rat	719 [47,50]
720	721 D2R	722 medial-poor	723 Mouse, Rat, Gerbil	724 [47]
725	726	727	728 <i>Drd2-eGFP, Drd2-Cre:RCE</i> mice	729 [35]
729	730 A2aR	731 medial-poor	732 <i>Drd2-Cre:RCE or LacZ-TauGFP</i> mice	733
734	735 PDE1b	736 medial-poor	737 Mouse, Rat, Gerbil	738 [47]
739	740 Enk	741 medial-poor	742 <i>Adora2a-Cre:YFP</i> mice	743 [35]
744	745 NT5E	746 medial-poor	747 <i>Pde1b-Cre</i> mice	748 [117](Gensat)
749	750	751 Enk	752 Mouse	753 [47,50]
754	755	756	757 <i>Penk-2A-CreERT2:tdTomato</i> mice	758 [48](Allen Brain Atlas)
759	760	761	762 <i>PPE-eGFP</i> mice	763 [49]
764	765	766 NT5E	767 Rat	768 [51]

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





