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Heterogeneity in dopamine neuron synaptic actions across the striatum and its relevance for schizophrenia

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Abstract

Brain imaging has revealed alterations in dopamine uptake, release and receptor levels in patients with schizophrenia that have been resolved at the scale of striatal subregions. However, the underlying synaptic mechanisms are at a finer scale. Dopamine neuron synaptic actions vary across the striatum, involving not only variations in dopamine release, but also in dopamine neuron connectivity, cotransmission, modulation and activity. Optogenetic studies have revealed that dopamine neurons release dopamine in a synaptic signal mode, and that the neurons also release glutamate and GABA as cotransmitters, with striking regional variation. Fast glutamate and GABA cotransmission convey discrete patterns of dopamine neuron activity to striatal neurons. Glutamate may function not only in a signaling role at a subset of dopamine neuron synapses, but also in mediating vesicular synergy, contributing to regional differences in loading of dopamine into synaptic vesicles. Regional differences in dopamine neuron signaling are likely to be differentially involved in the schizophrenia disease process, and likely determine the subregional specificity of the action of psychostimulants that exacerbate the disorder, and antipsychotics that ameliorate the disorder. Elucidating dopamine neuron synaptic signaling offers the potential for achieving greater pharmacological specificity through intersectional pharmacological actions targeting subsets of dopamine neuron synapses.

Keywords

glutamate; GABA; corelease; cotransmission; vesicular synergy; optogenetics; nucleus accumbens

Dopamine (DA) dysfunction is central to the pathophysiology of schizophrenia (1), with regional variations that likely shape schizophrenia symptoms. This idea arose with the early view that mesolimbic DA signaling mediated positive (psychotic) symptoms that could be treated with DA D2 receptor (D2R) antagonists, while blockade of nigrostriatal DA

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transmission accounted for extrapyramidal side effects, and possible worsening of negative (deficit) symptoms. Observations made in rats (2), and extended to non-human primates (3), showed that propsychotic psychostimulants, such as amphetamine, elicit the greatest DA release in the limbic or ventral striatum (vStr). With the impetus of adding serotonin 2A receptor blockade to antipsychotics, atypical antipsychotics emerged (4); they appeared to have fewer side effects due to more selective targeting of the vStr (5). However, vStr selectivity was challenged by more recent observations that DA release is increased in schizophrenia in the associative dorsal Str (dStr) where it correlates with positive symptoms, and diminished in the vStr where it correlates with negative symptoms (6, 7). These findings — although apparently contradictory — point to heterogeneity in dopamine function across the Str, and the importance of understanding regional differences in DA neuron synaptic actions. Mechanisms underlying regional differences in clinical imaging of DA release in schizophrenia can be investigated in rodents under similar baseline and pharmacological challenge conditions.

DA neurons, identified by the presence of the DA synthetic enzyme tyrosine hydroxylase (8), show significant functional heterogeneity. This heterogeneity is evident in differences in gene expression (9–11), electrophysiological properties (11, 12), projection-specific functions (13, 14), drug sensitivity (15), and vulnerability in neurodegenerative disorders (16, 17). Such heterogeneity is likely to be fundamental to understanding differential vulnerability in schizophrenia, as well as therapeutics. While electrochemical techniques have provided considerable insight into DA release and its variation (18), the synaptic actions of DA neurons have been harder to discern. Optogenetics has enabled selective targeting of DA neurons (19) to enable functional connectivity analyses (20, 21) that have now made the synaptic actions of these neurons accessible to study. In this review, we describe multiple dimensions of heterogeneity in DA neuron synaptic signaling in the Str and functional implications.

Striatal cytoarchitecture

The invariant Str cytoarchitecture — with about 95% GABAergic spiny projection neurons (SPNs), 5% GABAergic and cholinergic interneurons (ChIs), and prominent input from midbrain DA neurons and cortical and thalamic glutamatergic neurons (22–24) — engendered the early idea that the function of striatal circuits was homogenous across striatal regions. However, this view has been increasingly supplanted by findings of striatal heterogeneity.

Different striatal regions receive distinctly different excitatory inputs defining broad divisions into associative, sensorimotor and limbic domains (25, 26). The pattern of cortical inputs helps to define the correspondence between striatal regions in humans and rodents (Figure 1). The sensorimotor Str receives inputs from primary motor and premotor cortices and comprises in the primate the dorsolateral putamen and dorsolateral caudate (25, 27, 28), which corresponds to the lateral portion of the dorsal Str in rodents (26, 27, 29). The associative Str receives inputs from association areas of the cortex (dorsolateral prefrontal cortex) and comprises in the primate large parts of the rostral putamen and most of the head, body and tail of the caudate (25, 27, 28), and corresponds to the medial portion of the dorsal

Str in rodents (27, 30, 31). The vStr receives inputs from the hippocampus and amygdala, and from orbitofrontal and anterior cingulate cortices and comprises in the primate the nucleus accumbens (NAc) and ventral parts of the caudate and putamen (25, 27, 28, 32). In rodents, the vStr corresponds to the NAc and the striatal component of the olfactory tubercle (OT) (27, 30, 33). While the rodent NAc is subdivided into core and shell regions with different connectivity and function (34, 35), this division is not so clear in primates, although diffusion tractography identifies putative core (lateral-rostral NAc) and shell (medial-caudal NAc) divisions (36).

DA neurons project from the ventral midbrain to the Str topographically (Figure 2). Medial DA neurons in the ventral tegmental area (VTA) project predominantly to vStr. More lateral DA neurons in the substantia nigra (SN) project predominantly to associative and sensorimotor dStr domains (33, 37–39). Individual DA neurons target compact striatal domains that may subtend as much as 5% of the total striatal volume (40). The density of DAergic input to the striatal subregions is highest in the dStr and lowest in the NAc shell region of the vStr (41). Str SPNs project back to the ventral midbrain in a matching topology, predominantly targeting GABAergic neurons (21, 42), but also making connections to DA neurons (43, 44), with the exception of DA neurons projecting to the posterior Str that receive a wider range of inputs, from the globus pallidus, subthalamic nucleus and zona incerta (45).

Synaptic dopamine signaling in the striatum

DA signaling in the Str has been thought to be mediated mainly by diffusion of DA to extrasynaptic G-protein coupled DA receptors, that is by volume transmission (46, 47), engendering a range of modulatory effects, including the regulation of the excitability of SPNs and interneurons, and presynaptic regulation of excitatory input (46, 48–51). Modulatory actions of DA mediate longer time-scale control of motivational salience, vigor and social behavior (52 Gunaydin, 2014, 1535–1551, 53). However, DA neurons mediate faster, discrete DA synaptic responses, in addition to volume transmission.

In ventral midbrain slices, DA neurons produce sub-second D2R-mediated dendrodendritic inhibitory postsynaptic responses in neighboring DA neurons (54). Optogenetic studies have revealed subsecond DA synaptic responses in dStr brain slices (55) seen as a pause in the firing of ChIs and associated with a sub-second hyperpolarization (55, 56), mediated by a D2R coupling to G-protein coupled inward rectifier K⁺ channels (GIRKs) (55). D2R-mediated inhibitory postsynaptic currents (IPSCs) in Str ChIs have a latency of about 8 msec (55). Considering that the latency involves the time for channelrhodopsin 2 (ChR2) mediated depolarization (57), the activation of transmitter release machinery and G-protein coupled receptor transduction (slower than that of ionotropic receptors), the D2-IPSC is mediated monosynaptically. Although a D2-IPSC has not been reported in D2-SPNs, with GIRK2 transfection D2-IPSCs become detectable (58), indicating that DA neurons can elicit synaptic DA signals in projection areas, so long as D2Rs are proximate to DA release sites.

Dopamine neurons release multiple neurotransmitters

The possibility that DA neurons might exert fast actions via cotransmission was first suggested by the report of excitatory responses in the dStr evoked by stimulation of the nigrostriatal pathway (59). This observation was supported by detection of the glutamate synthetic enzyme glutaminase in DA neurons by immunocytochemistry (60). DA neuron glutamate cotransmission was demonstrated directly in microcultures of single identified rat VTA DA neurons (61), and monosynaptic DA neuron excitatory connections were subsequently detected in mouse brain slices (62), and shown to depend on the expression of vesicular glutamate transporter 2 (VGLUT2) (63). Then, with conditional expression of channelrhodopsin 2 (ChR2) in DA neurons (19), optogenetic stimulation of DA neuron terminals in the NAc showed that DA neurons mediate glutamatergic responses in the intact circuitry of the brain slice (55, 57, 64–66).

DA neurons also corelease GABA (67), derived in part from the action of glutamic acid decarboxylase (GAD), in part from uptake from the extracellular milieu via the plasma membrane GABA transporter 1 (mGAT1) (68), but mainly via synthesis by aldehyde dehydrogenase 1a1 (69). DA neurons do not express vesicular GABA transporter (VGAT); instead they load GABA into vesicles apparently mediated by the vesicular monoamine transporter 2 (VMAT2) (67, 68). In contrast to glutamate cotransmission, which is seen in a subset of DA neurons, most DA neurons appear capable of GABA cotransmission (68, 69). However, GABA IPSC amplitude declines rapidly with repeated stimulation at the *in vivo* firing frequency of DA neurons (56), so its role in fast DA neuron signaling remains to be demonstrated.

Regional heterogeneity in dopamine neuron synaptic actions

The three transmitters released by DA neurons — DA, glutamate and GABA — have different synaptic actions in different postsynaptic target neurons in different striatal subregions. Studies in brain slices from transgenic mice have so far focused on DA neuron connections to SPNs and ChIs in three Str regions, the NAc medial shell, NAc core and the dStr (Figure 3). DA neurons make the most prominent glutamatergic connections in the most medial, anterior part of the vStr, the medial shell (66). DA neuron glutamatergic connections to ChIs are the strongest, strong enough to drive firing without coincident excitatory inputs, while those to SPNs are weaker (55). GABA cotransmission is not seen in medial shell ChIs (55), which receive input from VTA GABA neurons (70). In the medial shell, following the burst in ChIs driven by DA neuron burst firing, ChIs show a post-burst hyperpolarization mediated by a sub-second D2R-mediated hyperpolarization, involving small conductance Ca²⁺ dependent K⁺ channels (SK channels), but not GABA (55). Interestingly, the olfactory tubercle (OT), which shares functions with the NAc medial shell (33), shows almost the same pattern of DA neuron transmission (65), differing only in the additional late contribution of a D5R-mediated burst (65).

In the NAc core, weak glutamate, GABA and fast D2R responses are observed in ChIs (55), but overall, DA neuron phasic firing drives a reduction in ChI firing (55) mediated by GABA cotransmission. Weak DA neuron GABA-mediated IPSCs are seen in SPNs (68, 69). In the

dStr, DA neurons drive a D2R-mediated pause in the firing of ChIs in the most medial anterior dStr (55). In one report, no clear glutamate or GABA cotransmission was seen (55), while in another GABA cotransmission and a slow excitatory synaptic current, mediated by an unidentified transmitter, were seen (56). Glutamate cotransmission was not observed in SPNs in the medial dStr in two studies in which VTA DA neurons were transfected with ChR2 (64, 66), while weak glutamate cotransmission was seen in two others in which lateral SNc DA neurons were transfected with ChR2 and recordings likely made in the more lateral dStr (67, 69). Thus, DA neuron glutamate cotransmission to SPNs appears to extend beyond the NAc to the lateral dStr, but not to the medial dStr; strong GABA cotransmission is observed in dStr SPNs, independent of glutamate cotransmission (56, 67, 68).

DA neuron glutamatergic responses are strong and invariably seen in NAc shell and olfactory tubercle (OT), and this correlates with DA neuron VGLUT2 expression in medial VTA DA neurons projecting to the NAc, while SN DA neurons projecting to the dStr do not express VGLUT2 (71, 72). This topography does not, however, align with recording of DA neuron glutamate cotransmission in lateral dStr SPNs; this could be mediated by the non-topographical DA neuron projection of medial dorsal VTA DA neurons to the lateral dStr, seen in rats (73, 74), and presumably also in mice. Thus, DA neuron synaptic connections to ChIs appear to encode DA neuron phasic firing positively in the medial shell and OT in the vStr, via glutamatergic signaling. In contrast, DA neuron synaptic connections to both ChIs and SPNs in the dStr encode DA neuron phasic firing negatively in the form of pauses mediated by inhibitory D2R and GABA signaling.

Regional heterogeneity in dopamine neuron synaptic terminals

Regional differences in DA release in schizophrenia could be due to alterations in DA neuron terminals. The match in increased F-DOPA uptake (7) and amphetamine-induced DA release in schizophrenia (6, 7) points to pathological presynaptic modulation of DA release (75). DA neuron transmission in the Str is modulated locally by presynaptic receptors (47, 76–78) that contribute significantly to regional heterogeneity. D2R potentially inhibit DA release (47), but there is no evidence for heterogeneity in autoreceptor function within the Str.

In contrast, presynaptic acetylcholine (ACh) receptors, which potentially drive DA release (79), show significant regional heterogeneity in their function, and have been extensively implicated in the pathogenesis of schizophrenia. Evidence for this extends from linkage to the $\alpha 7$ nicotinic receptor (80), extensive use of nicotine by patients (81), therapeutic potential of nicotinic cholinergic agonists (82), etiologic evidence for early developmental alterations in cholinergic balance (83), and postmortem evidence for altered cholinergic signaling in schizophrenia (84, 85). Nicotine-mediated desensitization shapes the balance between tonic and phasic firing on DA release, which may contribute to regional heterogeneity (86). Accentuation of DA neuron burst firing in the dStr may falsely emphasize less salient cue signals in patients with schizophrenia (87), while lower phasic DA release in the vStr, which correlates with negative symptoms, possibly contributes to disturbance in salience signals.

Synchronized ChI activity drives DA release in the dStr via nACh receptors on DA neuron terminals (88–90), while in the NAc ChI activity drives DA release through concerted activation of nicotinic and glutamate receptors. ChI terminals express auto-inhibitory muscarinic ACh receptors (mAChR), which reduce ACh release and temper nicotinic stimulation of DA release (91). Activation of nACh on DA neuron terminals or inhibition of mACh receptors on ChIs increases the DA release generated with single action potentials and limits DA release by subsequent action potentials in a burst (91). In contrast to the modest difference between single pulse-evoked and train-evoked DA release in the dStr (91, 92), DA release in the NAc shows robust frequency dependence, where nACh inhibition or mACh activation enhance frequency responsiveness (92–94). Reducing ACh synthesis in ChIs (95) or blockade of nACh receptors (86, 96) in the dStr enhances frequency responsiveness, showing the crucial contribution of nACh receptors to regional heterogeneity. Differences in nACh receptor subunit composition in DA neuron terminals projecting to the dStr and NAc, as well as mACh receptors in ChIs, likely contribute further to heterogeneity (91, 93, 94).

DA release is determined by vesicular loading, mediated by the vesicular monoamine transporter 2 (VMAT2) and modulated by VGLUT2, vesicular release, and reuptake, mediated by the DA transporter (DAT), all of which contribute to heterogeneity in DA release (78). Modulation of any of these steps can control DA release. VGLUT2 — which mediates glutamate cotransmission — also impacts vesicular DA loading (63) through vesicular synergy (97). VGLUT2-mediated glutamate uptake dissipates the vesicular electrical gradient enabling further activity of the vesicular proton pump, vesicular acidification and DA packing (47, 63, 98). Considering the prominent expression of VGLUT2 in VTA DA neurons, the contribution of vesicular synergy to DA release is likely to be most prominent in the NAc. Although there is clear evidence for the anatomical segregation of dopamine and glutamate release sites (99), this may not extend to all release sites, and estimates of segregation may be limited by the sensitivity of immunocytochemical detection.

Variation in presynaptic Ca²⁺ channels controlling release contribute to heterogeneity, with more channel types in dStr DA neuron terminals than in NAc terminals, as well as differences in Ca²⁺ buffering (100), conferring heterogeneous, complex frequency dynamics. In the non-human primate, release mechanisms *per se* show heterogeneity, with higher DA release probability in the dStr and lower probability in the vStr, estimated from differences in Ca²⁺ availability (101). DAT expression is higher in SNc compared to VTA DA neurons (102–104) so released DA is subject to more robust reuptake in the dStr than the NAc (105). Thus, heterogeneity in DA neuron presynaptic terminal function contributes strongly to regional variation in DA neuron signaling across the Str.

Regional heterogeneity in dopamine neuron activity

Heterogeneity in DA neuron signaling is driven by regional differences in the *in vivo* patterns of DA neuron firing. DA neuron firing depends on both intrinsic membrane properties and synaptic input (106). In brain slices, where most synaptic inputs to DA neurons are truncated, DA neurons show pacemaker firing at about 3–5 Hz (106). DA

neurons *in vivo* alternate between tonic and phasic firing, with bursts of about 5 spikes at 15–20 Hz, determined by patterns of synaptic input. Differences in intrinsic conductances determine the regularity and frequency of pacemaker firing (104). The pacemaker firing of DA neurons is driven by slow membrane potential oscillations (106, 107). The responsible intrinsic conductances differ between SNc and VTA DA neurons (107). In SNc DA neurons, slow oscillations are generated by low-threshold voltage-gated Ca²⁺ channels and SK channels (108, 109), while in VTA DA neurons, in addition to the contribution of SK channels, the depolarizing phase of the oscillation is shaped by two types of Na⁺ channels; non-voltage dependent leak currents and voltage-dependent tetrodotoxin-sensitive persistent currents (110).

Burst-firing shows regional heterogeneity with a gradient of decreasing burst firing from the VTA to the lateral SNc (111). Burst firing of DA neurons is driven by synchronous excitatory glutamate or nicotinic acetylcholine (nAChR) synaptic input; the medial-lateral gradient in burst firing is likely driven by regional differences in excitatory inputs. NMDA receptors are crucial for naturalistic burst firing in DA neurons (112), but their expression level shows a mediolateral gradient, opposite to the gradient in firing (113), and so does not account for the greater burst firing seen in VTA compared to SNc DA neurons (111). Modulation of intrinsic conductances can affect burst firing of DA neurons by changing overall excitability. Indeed, when the expression of SK3, the most prominent subtype of SK channels in DA neurons (108), is reduced in VTA DA neurons, *in vivo* firing of DA neurons increases and more bursting is observed (114). SK3 expression also shows a mediolateral gradient, with higher expression in lateral midbrain DA neurons (108, 115), and so correlates with the gradient in excitability. Thus heterogeneity in several intrinsic currents contributes to heterogeneity in the tonic and phasic firing of DA neurons, and thus to heterogeneity in their synaptic actions in the Str.

Regional increases in DA release in schizophrenia could be due to altered patterns of DA neuron activity. PET imaging of DA receptor ligand displacement reveals DA release (116) extending to the regional level in patients with schizophrenia (6), but has limited spatial as well as temporal resolution. Specifically, the relative contribution of tonic and phasic DA release to the increased DA signal seen in schizophrenia cannot be resolved due to limited temporal resolution. In the vStr of rodents, larger increases in DA release are driven by DA neuron bursting (117). Real-time electrochemical measurements in awake rats reveal further that time-averaged extracellular DA arises mainly from phasic release (118, 119). Thus, in the vStr, brain imaging of DA release likely reflects phasic DA neuron activity. In the dStr where DA release caused by single spike and burst firing are similar, and DA release does not show frequency potentiation (92, 94), the increased DA release in the associative Str in patients with schizophrenia (6) may reflect both higher tonic and phasic DA release. Possibly different dynamics in DA release in dStr versus vStr contribute to the greater increase seen in schizophrenia in the associative Str.

Regional differences in psychotropic drug action at striatal dopamine neuron terminals

Extrinsic neuromodulators, such as psychostimulants, act preferentially in vStr domains, in rodents as shown by microdialysis (2) and in non-human primates as shown by ligand displacement (3). In humans, the greatest amphetamine-induced ligand displacement is seen in the vStr and also in the sensorimotor Str (putamen) (120, 121). Consistent with the greater DA release in vStr in rodents, amphetamine and cocaine at lower doses appear to act preferentially in the vStr to drive hyperlocomotion, while at higher doses they act in the dStr to drive stereotypy (122–124).

A single exposure to amphetamine can significantly perturb Str DA neuron connections in a regionally and synaptically selective fashion (55). Low-dose amphetamine appears to affect glutamatergic connections in the NAc medial shell preferentially, while high-dose affects DA transmission across the Str. The relative sensitivity of NAc medial shell glutamate connections may impact DA release. Indeed, mice with a DA neuron conditional VGLUT2 deletion show an attenuated response to psychostimulants (63, 125). While this may be due to the dependence of DA neuron development on VGLUT2 expression (126), it may be due also to vesicular synergy. VGLUT2 mediates vesicular uptake of glutamate, which acting as a counter ion may enhance dopamine packaging, and confer increased sensitivity to amphetamine action. A further possibility is that the selective impact of amphetamine on DA neuron glutamate connections significantly alters their functional connectivity to ChIs in a manner commensurate with increased propensity to drug use. Interestingly, glutamate corelease in Str ChIs — mediated by VGLUT3 — also modulates psychostimulant sensitivity (127), but whether VGLUT3 is differentially distributed in ChIs has yet to be resolved. Conceivably, cotransmission preferentially sensitizes a subset of Str synapses to psychostimulants.

Antipsychotic drugs may exert regionally selective synaptic actions in the Str due to dynamics of vesicular uptake, exocytic release, and reuptake. As lipophilic weak-bases, most antipsychotic drugs accumulate in acidic organelles, including synaptic vesicles, where they are trapped by intraluminal protonation (128–130). This mechanism would lead to the concentration of antipsychotics at synaptic sites, as the drugs would accumulate in synaptic vesicles, undergo activity dependent release (130, 131), and then be taken back up, in an intrasynaptic recycling process. However, acidotropic uptake depends on vesicular acidity, and not on VMAT2 expression (130), so the accumulation is not specific to DA neurons (132–134). However, amphetamine, which acts selectively at DA neuron terminals, preferentially releases antipsychotic drugs from DA neuron synapses (130). And, DA neuron terminals in the vStr with more prominent expression of VGLUT2 are likely to show more robust acidification, as mentioned above. Antipsychotic drugs may preferentially — although not specifically — accumulate in DA neuron terminals in the vStr, and this may be important in determining their regional and dose-dependent actions in the Str. Determining the distribution of VGLUT2 in primate DA neurons will thus be important for evaluating the contribution of cotransmission to regional drug effects.

Implications of regional heterogeneity in dopamine neuron synaptic function for brain imaging and psychotropic drug action

The range of rodent studies we have discussed reveal striking regional heterogeneity in DA neuron synaptic actions at multiple levels that could underlie regional differences seen in brain imaging of dopamine function in schizophrenia. The finer detail in DA neuron synaptic transmission revealed by optogenetics indicates that DA neuron transmission involves a differential blend of three neurotransmitters and functions in Str subregions. The cotransmitters not only provide temporally precise information of DA neuron firing, particularly that of phasic firing, but also modulate striatal microcircuits by controlling ChI activity, which in turn feeds back on DA terminals, regulating DA neuron transmission. Heterogeneity in the influence of DA neuron activity on ChI activity likely plays a major role in regional differences in the dynamics of DA neuron signaling, shaping schizophrenia symptoms. Increased understanding of the cellular basis for regional drug action should inform interpretation of the brain imaging signal in schizophrenia, as well as enabling intersectional targeting of drugs to achieve better therapeutic effects with regional selectivity.

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Fig 1. Functional subdivisions of the striatum in humans and rodents

Functionally, the striatum (Str) can be divided into corresponding limbic (magenta), associative (green) and sensorimotor (blue) regions, in both human (left) and rodent (right), determined by cortical inputs mediating each function. The schematics shown are midway along the anterior-posterior axis; there are substantial phylogenetic differences both anteriorly and posteriorly (25, 73). The NAc, which makes up the vStr is indicated by the dashed lines. In mouse, a second dashed line indicates the border between the accumbens core and shell. Orientation of sections is indicated by arrows. Abbreviations; Cd: caudate, Pu: putamen, NAc: nucleus accumbens, dStr: dorsal striatum, OT: olfactory tubercle. Striatal outlines are modified from atlases (135, 136).

Fig 2. Topography of midbrain dopamine neuron projections to the striatum in rodents
DA neurons project topographically (indicated by color spectrum) along the medial-lateral axis. More medially located DA neurons in the VTA project to the ventral Str, the NAc medial shell and medial OT. More laterally located DA neurons project to more dorsolateral Str (33). The topography extends to primates (137).

Fig 3. Heterogeneity in DA neuron synaptic actions in the mouse striatum

Optogenetic stimulation of DA neuron terminals elicits fast synaptic responses in principal Str neurons, spiny projection neurons (SPNs) and cholinergic interneurons (ChIs). The relative strength of each transmitter response in different Str regions is shown in pie charts. For reports without details of recording locations, the pie chart is located at the center of the region (e.g., dStr, Ref. 56). Responses seen in each area are schematized in pie charts by color: DA D2 receptor (dark green), DA D1 receptor (light green), GABA_A receptor (dark blue), ionotropic glutamate receptor (magenta), and unknown excitatory transmitter (gray). Striatal outlines are the same as used in Figure 1. The schemes are a compendium of the several optogenetic studies (56, 62, 65–68).