Review

Biological Psychiatry

Pathway-Specific Dopamine Abnormalities in Schizophrenia

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ABSTRACT

In light of the clinical evidence implicating dopamine in schizophrenia and the prominent hypotheses put forth regarding alterations in dopaminergic transmission in this disease, molecular imaging has been used to examine multiple aspects of the dopaminergic system. We review the imaging methods used and compare the findings across the different molecular targets. Findings have converged to suggest early dysregulation in the striatum, especially in the rostral caudate, manifesting as excess synthesis and release. Recent data showed deficit extending to most cortical regions and even to other extrastriatal subcortical regions not previously considered to be "hypodopaminergic" in schizophrenia. These findings yield a new topography for the dopaminergic dysregulation in schizophrenia. We discuss the dopaminergic innervation within the individual projection fields to provide a topographical map of this dual dysregulation and explore potential cellular and circuit-based mechanisms for brain region–dependent alterations in dopaminergic parameters. This refined knowledge is essential to better guide translational studies and efforts in early drug development.

Keywords: Cortex, Dopamine, Neuroanatomy, PET imaging, Schizophrenia, Striatum

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HISTORICAL PERSPECTIVE ON DOPAMINE RESEARCH IN SCHIZOPHRENIA

Dopamine (DA) has been a focus of schizophrenia (SZ) research for decades, yielding two prior conceptual formulations for involvement of DA in SZ. In 1966, Rossum (1) proposed a state of excess dopaminergic stimulation in patients with SZ, which was substantiated later by the discovery of the D_2 receptor binding profiles of antipsychotics and the psychotogenic effects of DA agonists (2–4). This state of excess dopaminergic stimulation was later reformulated as an imbalance between excess subcortical DA and a deficit in cortical DA, in light of evidence suggesting a prefrontal cortical deficit in SZ and the prominent role of DA in mediating prefrontal-dependent cognitive processes (5,6). The availability of imaging tools to measure aspects of dopaminergic transmission in vivo allowed testing of these formulations in patients. Improved scanner technology enabled better anatomic resolution. Earlier detection and awareness of the prodromal phase of the disease (7,8) resulted in testing earlier stages of SZ (9–11), whereas stress paradigms (12,13) allowed probing responsiveness of the system to a relevant risk factor for the disease (14,15), together yielding a replicable set of findings across laboratories documenting excess presynaptic dopaminergic transmission in the striatum, confirming the original formulation. Furthermore, data from our laboratory provided new evidence for a cortical DA deficit (16), supporting the second formulation but also expanding it to multiple extrastriatal regions not previously considered to be "hypodopaminergic" in SZ.

The topic of this review is a new topographical mapping of DA dysregulation in SZ. First, we describe the imaging methods used to examine dopaminergic indices and findings in SZ. We then review dopaminergic innervation and its imaging-relevant targets within individual projection fields to provide a topographical map of the findings and suggest potential mechanisms for brain region–dependent DA dysregulation in SZ. Finally, we discuss future directions.

METHODOLOGY FOR IMAGING THE DA SYSTEM

Positron emission tomography (PET) and single photon emission computed tomography (SPECT) have been used to measure DA-related parameters via administration of radioligands that bind to receptors, transporters, or other target molecules or, alternatively, that trace a metabolic pathway. For radioligands that reversibly bind to receptors, the most commonly derived parameter is the binding potential (BP) (17,18), which is proportional to B_{AVAIL}/K_D, where B_{AVAIL} is the concentration of the target molecule available for binding to the radiotracer, and K_D is the equilibrium dissociation constant of tracer for the target. There are several versions of BP, depending on which concentration of tracer is used as a reference value. For the frequently used binding potential relative to the nondisplaceable compartment (BP_{ND}) (Figure 1A–C), the reference is the nondisplaceable compartment, composed of the sum of the free plus nonspecifically bound radiotracer in brain; $BP_{ND} = f_{ND} * B_{AVAIL}/K_D$, where f_{ND} is the free fraction of the nondisplaceable radiotracer

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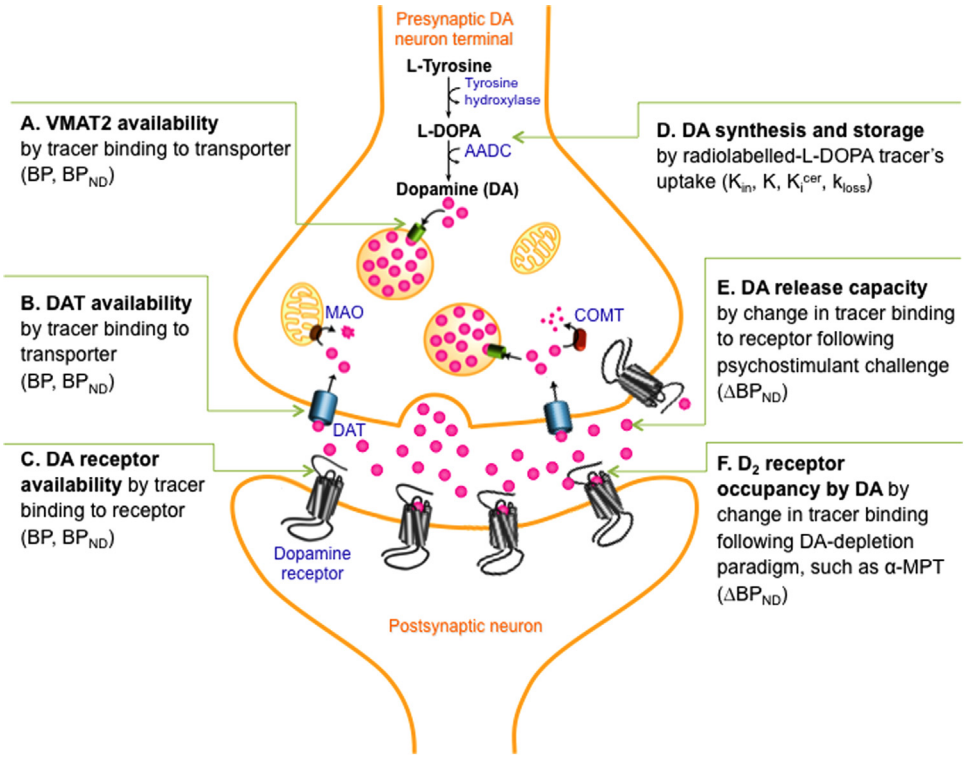

Figure 1. Dopaminergic imaging targets. Schematic of imaging methods used to measure aspects of the dopamine system in vivo. Graphic depicts progression of dopamine from synthesis **(D)**, storage **(A)**, to release **(E, F)**, then either reuptake by dopamine transporter **(B)** or binding to receptor **(C)**. Imaging targets and related paradigms are described in the text. AADC, amino acid decarboxylase; α-MPT, alpha-methyl-para-tyrosine; BP, binding potential; BP_{ND}, binding potential relative to the nondisplaceable compartment; ΔBP_{ND}, percent change in BP_{ND} between conditions; COMT, catechol-O-methyltransferase; DA, dopamine; DAT, DA transporter; K_{in}, steady state [^{18}F]DOPA uptake rate constant; K, steady state [^{18}F]DOPA uptake rate constant as defined by Kumakura *et al.* (35); K_i^{cer}, K_{in} relative to [^{18}F]DOPA concentration in cerebellum; k_{loss}, brain efflux rate constant for [^{18}F]DOPA metabolites; MAO, monoamine oxidase; VMAT2, vesicular monoamine transporter 2.

concentration. BP_{ND} is an indicator of target molecule availability, based on the assumption that K_D and f_{ND} are not different across groups. B_{AVAIL}, as opposed to the total target concentration B_{MAX}, accounts for the masking of some of the targets by the binding of endogenous ligands. BP_{ND} is also the ratio of specifically bound to nondisplaceable radiotracer concentrations at equilibrium, representing the associated signal-to-noise ratio [see Innis *et al.* (17) for complete definitions]. A BP_{ND} <0.5 (i.e., signal lower than half of background) is considered too low to provide meaningful information.

Tracers with moderate affinity for DA D_2–like receptors (D_2 and D_3 receptors, hereafter referred to as D_2), such as [^{11}C]raclopride and [^{123}I]iodobenzamide, provide reliable BP_{ND} in the striatum (Figure 1C). [^{18}F]Fallypride has an order of magnitude higher affinity (19,20) and provides reliable quantification in striatum, thalamus, midbrain, hippocampus, amygdala, and temporal cortex. Higher affinity tracers, such as [^{11}C]FLB457 (21) or [^{123}I]epidepride (22), can be used to quantify D_2 density in cortex, although their equilibration is prohibitively slow for quantification in striatum. Pharmacologically, all these tracers are antagonists. [^{11}C]-(+)-PHNO is a D_3 preferring agonist (23–25). Tracers for D_1-like receptors (D_1 and D_5 receptors, hereafter D_1) include [^{11}C]NNC112 and [^{11}C]SCH23390 (26,27). Both tracers have been used to quantify D_1 in cortex and striatum, although the BP_{ND} of [^{11}C]SCH23390 is <0.5 in cortex.

Tracers for D_2 receptors are sensitive to changes in the concentration of DA through competitive interaction. Pharmacologic challenges that increase synaptic DA, such as concomitant release and reuptake blockade by amphetamine or reuptake blockade by methylphenidate, decrease BP_{ND}, whereas depletion paradigms that reduce baseline synaptic DA, such as blockade of tyrosine hydroxylase activity with alpha-methyl-para-tyrosine, increase BP_{ND}. These effects can be quantified as ΔBP_{ND}, the percent change of BP_{ND} across conditions (Figure 1E, F). D_2 ligand displacement by challenge-induced DA release occurs at the subset of D_2 receptors that are in close proximity to DA release sites (28–32). This has led to the postulation that net change in tracer binding at these perisynaptic receptors may comprise the PET "DA release" signal (33), which refers to our PET measurement of intrasynaptic DA levels, either evoked (as a result of amphetamine administration) or basal (measured with the depletion paradigm).

[^{18}F]DOPA is a substrate for amino acid decarboxylase, which catalyzes L-dihydroxyphenylalanine (DOPA) into DA (34). In terminals containing amino acid decarboxylase, [^{18}F]DOPA is converted to 6-fluorodopamine ([^{18}F]6-FDA), a substrate for vesicular monoamine transporter 2 (VMAT2), which loads presynaptic DA into vesicles (Figure 1D). [^{18}F]6-FDA cycles through exocytosis, reuptake through the DA transporter (DAT), and reloading into vesicles. This is generally treated as an irreversible process. The outcome measure is K_{in}, the steady-state uptake rate constant of the tracer, characterizing [^{18}F]6-FDA formation when the concentration of [^{18}F]DOPA in arterial plasma and in brain are at a hypothetical steady state. K_{in} indicates the capacity for DA synthesis. A related outcome measure is K_i^{cer}, which is the steady-state uptake rate (K_{in}) relative to cerebellum concentration of [^{18}F]DOPA, rather than the arterial plasma concentration, but studies using K_i^{cer} require the implicit assumption that concentration of [^{18}F]DOPA in the cerebellum does not differ between groups.

Quantification of [^{18}F]DOPA is complicated by formation in the periphery of the radiolabeled metabolite 3-*O*-methyl-FDOPA as a result of catechol-*O*-methyltransferase activity (35); pretreatment with entacapone can reduce this effect. In addition, the irreversibility of [^{18}F]DOPA uptake is an idealization, as [^{18}F]6-FDA is a substrate for both monoamine oxidase and catechol-*O*-methyltransferase, and metabolites diffuse out of the brain, affecting measurement of K_{in}. Some models account for this washout with an estimated parameter called k_{loss} (35,36).

[^{18}F]DOPA K_{in} can be measured in striatum, but extrastriatal K_{in} is lower and more difficult to measure. In substantia nigra (SN), K_{in} is approximately half as large as in striatum; in cortex, it is too low to be interpretable (37). Transporters have also been imaged using (+)-alpha-[^{11}C]dihydrotetrabenazine ([^{11}C]DTBZ) for VMAT2 (38) (Figure 1A), [^{11}C]PE2I for DAT (Figure 1C) in striatal and extrastriatal regions using PET, and [^{123}I]βCIT (39) for striatal DAT using SPECT.

IMAGING THE DA SYSTEM IN SZ

We review findings from studies that used molecular neuroimaging to investigate the DA system in vivo in SZ—first in striatum, then in extrastriatal regions—with a focus on cortex and midbrain (Supplemental Table S1).

Striatum

Presynaptic. Higher striatal [^{18}F]DOPA was first reported in psychosis related to epilepsy and SZ (40). Seven studies replicated this finding in SZ (9,41–47), whereas two did not (48,49), and subsequent meta-analyses confirmed the finding (50,51). Using D_2 radiotracers and a psychostimulant challenge, four studies showed higher release in the striatum of antipsychotic-free patients compared with healthy control (HC) subjects (52–55). Excess DA release correlated with transient stimulant-induced worsening of psychotic symptoms in patients and was observed at disease onset and during exacerbations but not during periods of remission (56). Furthermore, baseline synaptic DA assessed with a depletion paradigm (57) were enhanced in striatum in SZ and were correlated with amphetamine-induced release in a cohort of antipsychotic-naïve patients (58). Using a higher resolution scanner and more sophisticated region-of-interest analysis methods to identify the striatal substructures, we later demonstrated that excess striatal DA was most prominent in the rostral caudate (59). In the associative striatum (AST), which contains the rostral caudate, rostral putamen, and postcommissural caudate, the effect size was 0.70 compared with 0.14 in the limbic striatum (or ventral striatum) and 0.34 in the sensorimotor striatum (SMST) (or posterior putamen). This excess does not seem to be related to excess dopaminergic innervation, as VMAT2 (60,61) and DAT (62–72) were normal.

Postsynaptic. Several studies have examined striatal D_2 availability. A meta-analysis of 23 studies showed small elevation and greater variability in SZ. When analysis was limited to antipsychotic-naïve patients, patients with SZ and HC subjects did not differ (51), suggesting that D_2 increases in striatum in SZ may be due to prior antipsychotic treatment. Striatal D_1 availability is also normal in SZ (27,73–75).

Further support for antipsychotic-induced upregulation of striatal D_2 derives from alpha-methyl-para-tyrosine studies (57–59), which provide a direct measure of "true" D_2 density by unmasking the fraction of receptors bound by endogenous DA. A new analysis of these previously published studies shows that unmasked BP_{ND} is higher (by 10%–20%) in previously medicated, but not antipsychotic-naïve, patients compared with HC subjects (Table 1) in striatum (57–59) and in rostral caudate (59). In contrast, in the same cohorts, alpha-methyl-para-tyrosine–induced ΔBP_{ND} showed that striatal DA levels are 65%–120% higher in both antipsychotic-naïve and previously medicated patients compared with HC subjects. This finding suggests that striatal dopaminergic hyperactivity

Table 1. Effect of Previous Antipsychotic Exposure on Unmasked BP_{ND}: Binding Potentials From Alpha-Methyl-Para-Tyrosine Depletion Studies

	HC, *n* or Mean ± SD	SZ, *n* or Mean ± SD	*p*	Rx-Free, *n* or Mean ± SD	Rx-Naïve, *n* or Mean ± SD	Rx-Free vs. Rx-Naïve, *p*	Rx-Free vs. HC, *p*	Rx-Naïve vs. HC, *p*
[^{123}I]IBZM SPECT: Striatum[a]	*n* = 18	*n* = 18		*n* = 10	*n* = 8			
BP_{ND}Bsl	0.722 ± 0.091	0.751 ± 0.103	.38	0.779 ± 0.122	0.716 ± 0.066	.21	.17	.87
BP_{ND}Dpl[b]	0.787 ± 0.096	0.889 ± 0.124	.009	0.930 ± 0.147	0.837 ± 0.062	.12	.004[c]	.19
[^{11}C]Raclopride PET: Striatum[d]	*n* = 18	*n* = 18		*n* = 12	*n* = 6			
BP_{ND}Bsl	2.53 ± 0.25	2.56 ± 0.52	.83	2.71 ± 0.50	2.25 ± 0.44	.08	.19	.07
BP_{ND}Dpl[b]	2.81 ± 0.23	2.94 ± 0.54	.35	3.12 ± 0.52	2.59 ± 0.42	.048	.04[c]	.12
[^{11}C]Raclopride PET: Rostral Caudate[d]	*n* = 18	*n* = 18		*n* = 12	*n* = 6			
BP_{ND}Bsl	2.40 ± 0.23	2.41 ± 0.45	.89	2.54 ± 0.43	2.16 ± 0.42	.10	.25	.10
BP_{ND}Dpl[b]	2.61 ± 0.27	2.77 ± 0.49	.25	2.91 ± 0.47	2.47 ± 0.43	.07	.03[c]	.36

BP_{ND}, binding potential relative to the nondisplaceable compartment; BP_{ND}Bsl, D_2 BP_{ND} in baseline state, partially masked by baseline levels of endogenous dopamine; BP_{ND}Dpl, unmasked D_2 BP_{ND} in the dopamine-depleted state; HC, healthy control participants; IBZM, iodobenzamide; PET, positron emission tomography; Rx-free, antipsychotic-free, previously medicated patients; Rx-naïve, antipsychotic-naïve patients; SPECT, single photon emission computed tomography; SZ, patients with schizophrenia.

[a]Abi-Dargham *et al.*, 2000 (57).

[b]Significant one-way analysis of variance comparing BP_{ND}Dpl for Rx-free, Rx-naïve, and HC ($p < .05$).

[c]Significant post hoc *t* test for BP_{ND}Dpl, Rx-free compared with HC (but not significant for Rx-naïve compared with HC).

[d]Kegeles *et al.*, 2010 (59).

is present regardless of prior antipsychotic treatment and thus a more reliable index of DA dysregulation than receptor upregulation.

Clinical Correlates of Striatal Findings. The striatal dopaminergic hyperactivity in SZ is associated with the psychotic symptoms of the illness. It was shown to extend to physiologic conditions under psychosocial stress and to be most enhanced in AST and SMST in antipsychotic-naïve patients and in the prodrome (14). Elevated striatal [^{18}F]DOPA uptake also precedes the onset of psychosis (76); correlates with greater severity of prodromal symptoms and neuropsychological impairment; predicts conversion; and, in both the prodrome and SZ, relates negatively to prefrontal cortical activation during cognitive tasks (43,77) [but also see Fusar-Poli *et al.* (78)]. It is also predominant in the AST (79,80).

Furthermore, excess striatal DA predicts treatment response of psychosis to antipsychotics (58) and is higher in patients who respond to antipsychotics (81). Patients with SZ (82) and individuals at clinical high risk for SZ (11) with comorbid substance use display a blunted striatal DA release. However, despite this presynaptic blunting, D_2 receptors remain supersensitive to stimulation, leading to psychosis. This suggests two distinct alterations in psychosis: excess presynaptic release in striatum and a functional supersensitivity of striatal D_2.

Cortex

Presynaptic. Using [^{11}C]FLB457, we showed significant blunting of DA release throughout the cortex in SZ. DA release in the dorsolateral prefrontal cortex was significantly positively associated with working memory–related blood oxygen level–dependent activation, suggesting a relationship between blunted release and deficits of frontal cortical function (16). [^{18}F]DOPA (45–48) reports in the cortex are uninterpretable (37).

Postsynaptic. D_2 availability in SZ is normal in prefrontal (16,83–85), occipital (16,84), parietal (16,84), entorhinal (86), anterior cingulate (16,83,87) [exception in Suhara *et al.* (84)], and insular (16,86) cortices. A meta-analysis [excluding Slifstein *et al.* (16)] found no differences in temporal cortex (88). One study reported lower binding in uncus (87), whereas another did not (16).

Studies of prefrontal cortical D_1 availability in SZ yielded inconsistent results of increases (74,75) and decreases (27) compared with HC subjects (Supplemental Table S1). To reconcile these findings, both D_1 tracers were examined in the same subjects (89,90) and showed similar alteration using either tracer, suggesting cohort-related effects rather than tracer differences. Prior exposure to antipsychotics may explain some of these discrepancies, as higher D_1 levels were observed only in antipsychotic-naïve patients, and duration of antipsychotic-free interval positively correlated with higher binding in previously treated patients (75).

Extrastriatal Subcortical Regions and Midbrain

Presynaptic. [^{18}F]DOPA uptake in SZ is normal in thalamus (47) and entorhinal cortex (47) but enhanced in amygdala (46) and midbrain (46,91). One study reported higher [^{18}F]DOPA utilization (K) and turnover (k_{loss}) in midbrain, whereas K_{in} was numerically lower (46). Another reported higher K_i^{cer} in the midbrain, which correlated with symptom severity in SZ (91) and predicted conversion in subjects with clinical high risk for SZ (92). We measured significant blunting of amphetamine-induced DA release measured by [^{11}C]FLB457 displacement in extrastriatal subcortical regions including midbrain (16). Thus, for the amygdala and midbrain, PET indices of presynaptic DA synthesis and turnover and amphetamine-evoked DA release seem discrepant. If this discrepancy is true, it may suggest elevated enzymatic activity in the presence of lower cytoplasmic and vesicular pools of DA in midbrain in SZ (see subsequent discussion).

Using [^{11}C]PE2I, one study reported higher DAT in the thalamus but not in SN (72). However, the small sample size and low BP_{ND} suggest caution in interpreting this study. VMAT2 was normal in extrastriatal regions (61) except for ventral midbrain, where an increase was reported (93); however, as BP_{ND} was <0.5, this finding should also be considered with caution.

Postsynaptic. Of the nine studies in thalamus (16,84–87,94–97), only one [Lehrer *et al.* (94), which overlaps with Buchsbaum *et al.* (98)] found lower D_2 in SZ, and a meta-analysis (88) was negative. Likewise, no differences were found in globus pallidus (97), amygdala (16,86,87), entorhinal cortex (16,86), or hippocampus (84,86,87). In SN, normal (16,86,97,99), higher (87), and lower (96) D_2 availability was reported, and a meta-analysis (88) was negative. No differences in D_1 availability have been observed in extrastriatal subcortical regions of interest (Supplemental Table S1).

Summary of Imaging Findings

Four main dopaminergic alterations have emerged in SZ: 1) DA synthesis and release capacity are increased in the striatum (51). 2) Although needing replication, DA release capacity in prefrontal cortical and other extrastriatal regions is decreased (16). 3) There is subregional heterogeneity in the DA dysregulation within the striatum. The rostral caudate and the AST in general show lower DA release capacity than the SMST in HC subjects (100), but not in patients with SZ because of a prominent increase in the AST (9,14,59). Supportive evidence for the prominent role of DA dysregulation in AST also derives from studies of prodrome (9,14). 4) Postsynaptic receptors and transporters do not show a reliably detectable altered expression either in the striatum or in extrastriatal regions of the brain in SZ.

TOPOGRAPHY AND SYNAPTIC CHARACTERISTICS OF DOPAMINERGIC PROJECTIONS

To understand the abnormal PET DA signal in SZ, we consider the regional anatomic factors that may affect it. We review the complex topography and chemical neuroanatomy of DA systems underlying PET indices of basal and evoked DA release.

DA projections comprise the retrorubral field (A8), SN (A9), and ventral tegmental area (A10) (Figure 2) (101–103). These

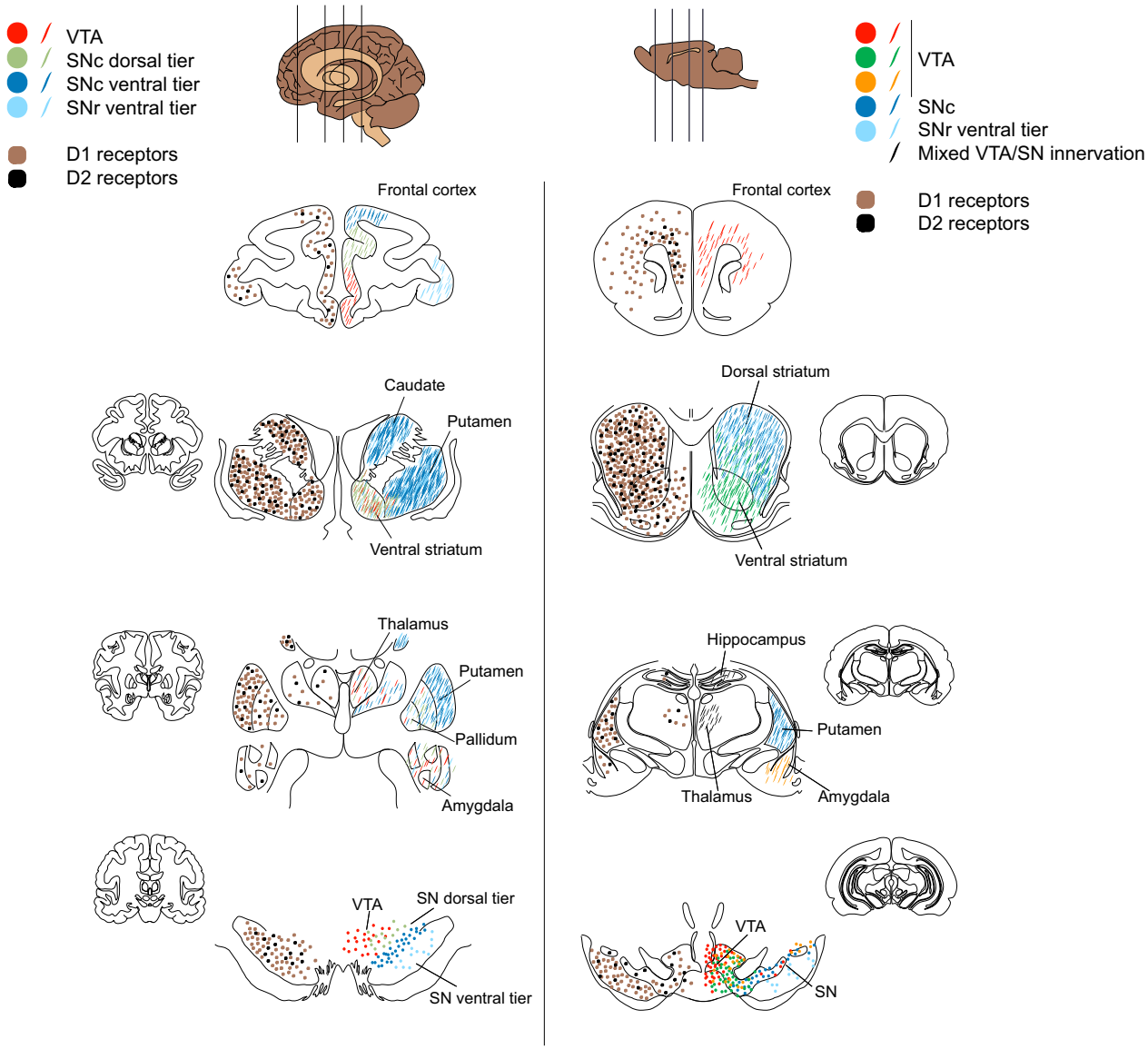

Figure 2. Topography of dopaminergic innervation and receptor distribution. Schematic representation of distributions of dopamine (DA) D_1 and D_2 receptors (left hemispheres) and patterns of dopaminergic innervations (right hemispheres) in select primate (left panel) and rodent (right panel) brain regions. *Left hemispheres*: Brown and black squares depict D_1 and D_2 receptors, respectively. Throughout the primate and rodent brain, D_1 receptors are present at a higher density than D_2 receptors. The striatum, in particular the caudate-putamen, has the highest densities of DA receptors. DA receptors are also present in medium to low densities in the cortex, pallidum, and midbrain. Receptor densities are relatively low in thalamus, amygdala, and hippocampus. See text for details. *Right hemispheres*: Topographical distribution of DA cell bodies (filled circles) and their terminals (lines). In the primate panel, red circles represent DA cell bodies in the ventral tegmental area (VTA) with terminals in the cortex, striatum (in particular, the ventral part), pallidum, thalamus, and amygdala. The VTA dopaminergic cellular organization is better characterized in the rodent where discrete VTA cell groups project to the cortex (red), nucleus accumbens (dark green), and amygdala (orange). In the primate brain, substantia nigra (SN) dorsal tier cell group (light green) projects to the cortex and ventral striatum as well as the pallidum, thalamus, and amygdala. The rodent brain, in contrast, has a low density of these dorsal tier neurons. The SN ventral tier groups (SN compacta densocellular part [dark blue] and fingers [light blue]) project heavily and topographically to caudate-putamen with medium to low innervations of cortex, ventral striatum, thalamus, and amygdala. See text for further details. SNc, SN pars compacta; SNr, SN pars reticulata.

areas have different intrinsic properties and afferents regulating spike activity; synthesis, release, or reuptake of DA; and postsynaptic effects (101–104) (Figure 3). Dorsal tier DA neurons, a band along the dorsal SN pars compacta (SNc) and contiguous regions of ventral tegmental area and retrorubral field, project to cerebral cortex, ventromedial striatum, pallidum, "extended amygdala," and thalamus. The ventral tier neurons, including the densocellular region of the SNc and DA cell columns within the SN pars reticulata (SNr), project to the striatum. The SMST receives a dense projection, with high density of DA release sites (104), accounting for the higher PET DA release signal, and highest levels of DAT, exerting

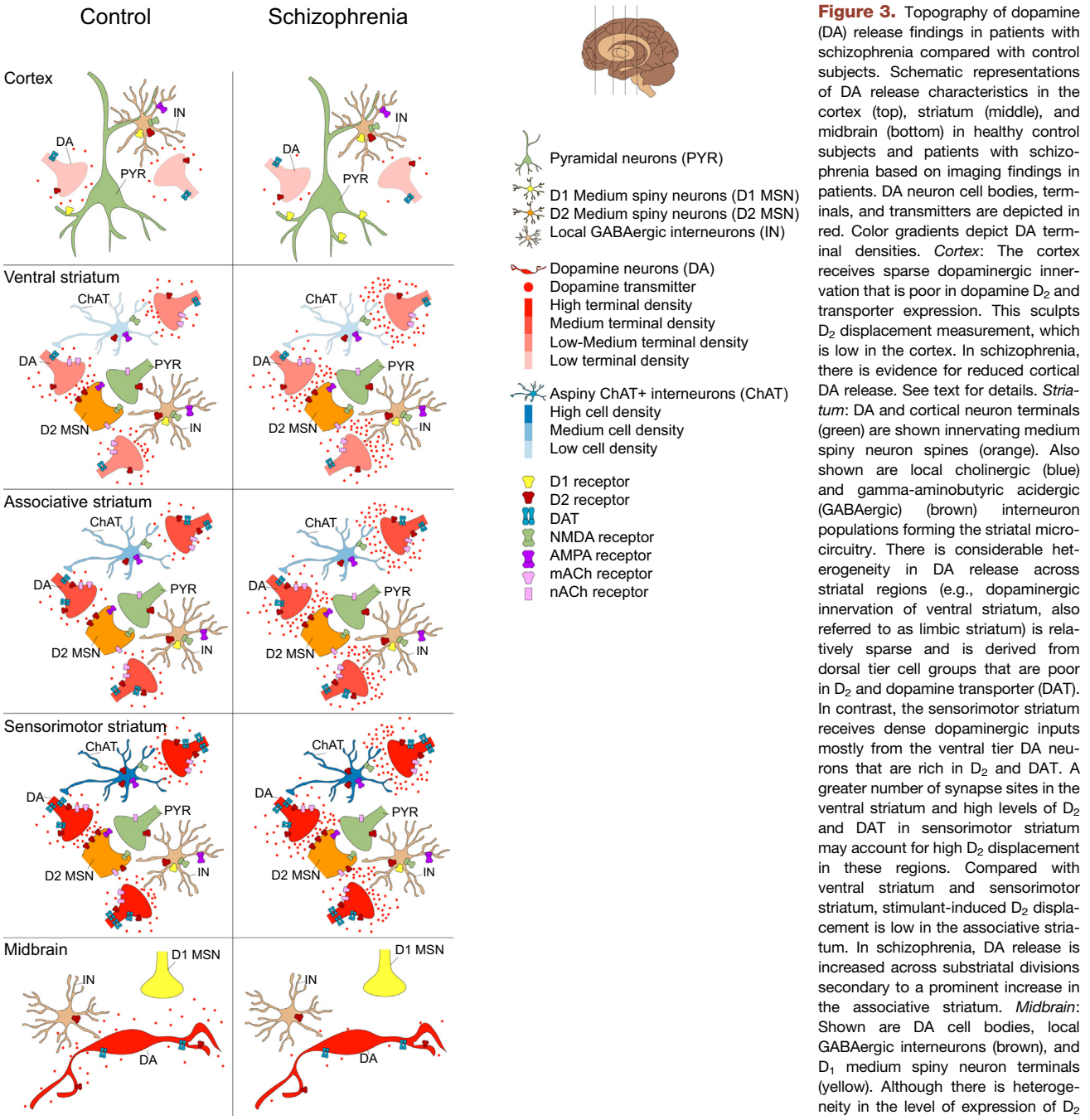

Figure 3. Topography of dopamine (DA) release findings in patients with schizophrenia compared with control subjects. Schematic representations of DA release characteristics in the cortex (top), striatum (middle), and midbrain (bottom) in healthy control subjects and patients with schizophrenia based on imaging findings in patients. DA neuron cell bodies, terminals, and transmitters are depicted in red. Color gradients depict DA terminal densities. *Cortex*: The cortex receives sparse dopaminergic innervation that is poor in dopamine D_2 and transporter expression. This sculpts D_2 displacement measurement, which is low in the cortex. In schizophrenia, there is evidence for reduced cortical DA release. See text for details. *Striatum*: DA and cortical neuron terminals (green) are shown innervating medium spiny neuron spines (orange). Also shown are local cholinergic (blue) and gamma-aminobutyric acidergic (GABAergic) (brown) interneuron populations forming the striatal microcircuitry. There is considerable heterogeneity in DA release across striatal regions (e.g., dopaminergic innervation of ventral striatum, also referred to as limbic striatum) is relatively sparse and is derived from dorsal tier cell groups that are poor in D_2 and dopamine transporter (DAT). In contrast, the sensorimotor striatum receives dense dopaminergic inputs mostly from the ventral tier DA neurons that are rich in D_2 and DAT. A greater number of synapse sites in the ventral striatum and high levels of D_2 and DAT in sensorimotor striatum may account for high D_2 displacement in these regions. Compared with ventral striatum and sensorimotor striatum, stimulant-induced D_2 displacement is low in the associative striatum. In schizophrenia, DA release is increased across substriatal divisions secondary to a prominent increase in the associative striatum. *Midbrain*: Shown are DA cell bodies, local GABAergic interneurons (brown), and D_1 medium spiny neuron terminals (yellow). Although there is heterogeneity in the level of expression of D_2 receptors and DAT (e.g., dorsal tier and especially medial ventral tegmental area neurons have low D_2 and DAT levels), imaging studies showing subregional analysis of D_2 displacement are lacking. However, in schizophrenia, there is a reduced stimulant-induced D_2 displacement. AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; ChAT, choline acetyltransferase; D_1, D_1 receptor; D_2, D_2 receptor; mACh, muscarinic acetylcholine; nACh, nicotinic acetylcholine; NMDA, *N*-methyl-D-aspartate.

tighter spatiotemporal regulation of DA diffusion compared with other subregions. The ventral striatum, innervated by ventral tegmental area and medial SNc DA neurons, has lower DA release potential and lower levels of DAT and D_2 autoreceptors (105,106). The AST receives a mosaic of dorsal and ventral tier neurons.

The SMST, AST, and ventral striatum also differ in glutamatergic, cholinergic, and other local (e.g., opioidergic) modulation of DA release, owing to neurochemically distinct compartments within each of these subregions, called patch (or striosome) and matrix. These refer to a "mosaic" pattern of grouping of neurons that have differential neurochemical

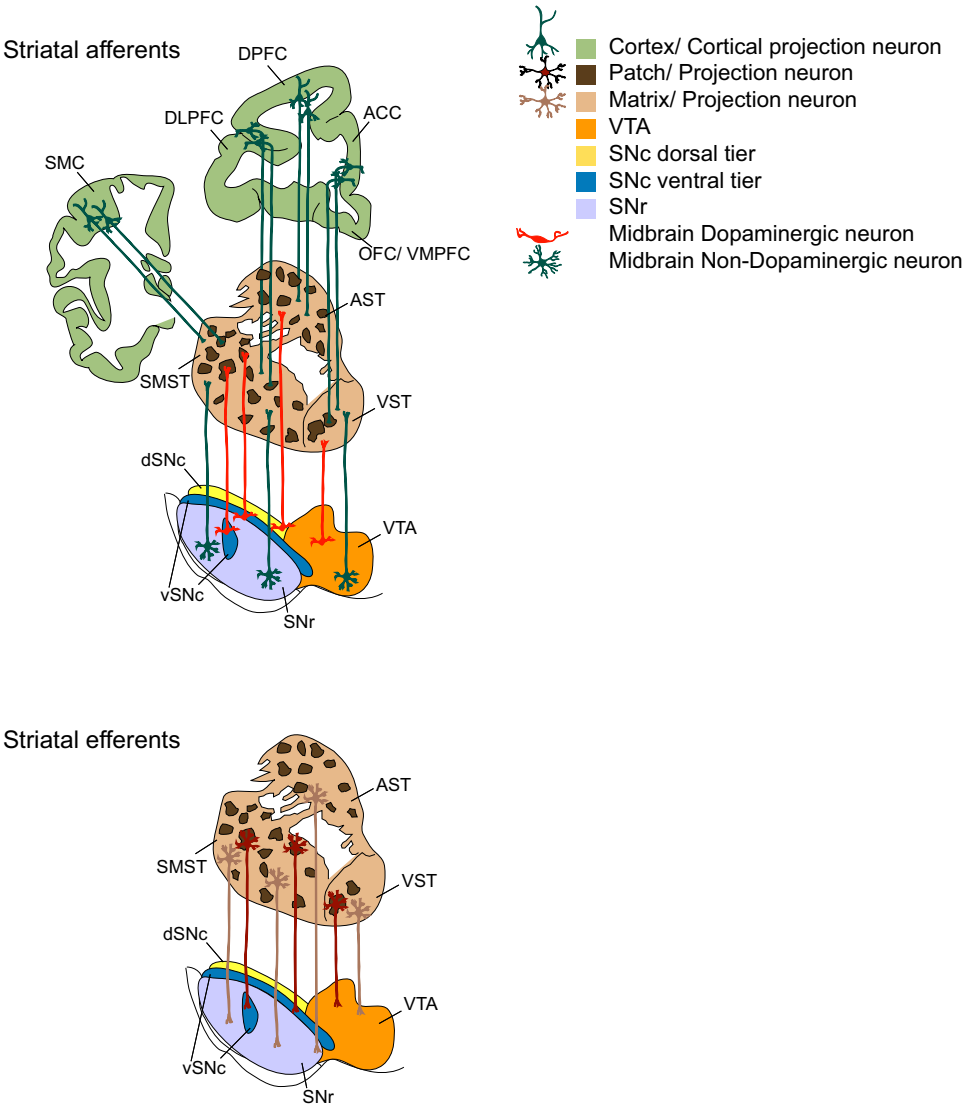

Figure 4. Striatal patch-matrix connectome. Schematic representation of striatal patch-matrix connectome. *Afferents*: The cortex topographically projects to the striatum. Within the cortex, deeper cortical layers innervate striatal patches (dark brown), whereas the surrounding matrix (light brown) is innervated by superficial cortical layers (light brown). Within the midbrain, the dorsal tier (orange and yellow) innervates the matrix, as do the nondopaminergic cells (dark green) from the same region. Patch innervation from the midbrain is mostly derived from the ventral tier cell groups (dark blue). Nondopaminergic (presumably gamma-aminobutyric acidergic) projection neurons within the substantia nigra pars reticulata (SNr) innervate the striatal matrix complex. *Efferents*: Striatal patch neurons (maroon) mostly project to ventral tier dopamine (DA) cells. These include both D_1 receptor–expressing medium spiny neurons and other striatal projection neurons. Striatal projection neurons within the matrix project to both dopamine and nondopaminergic populations within the dorsal tier and gamma-aminobutyric acidergic populations in the SNr. See text for further details. ACC, anterior cingulate cortex; AST, associative striatum; DLPFC, dorsolateral prefrontal cortex; DPFC, dorsal prefrontal cortex; dSNc, dorsal tier substantia nigra pars compacta; OFC/VMPFC, orbitofrontal cortex/ventromedial prefrontal cortex; SMC, sensorimotor cortex; SMST, sensorimotor striatum; SNc, SN pars compacta; vSNc, ventral tier SN pars compacta; VST, ventral striatum; VTA, ventral tegmental area.

characteristics and specific connections to cortex and other brain regions (Figure 4). In the SMST, the ventral tier DA neurons innervate both the mu opioid receptor and substance P–rich "patch" and the enkephalin-rich "matrix" compartments; in the AST, ventral tier innervation is selective to patches. This has implications for DA modulation of cortical afferents, as patches receive projections from limbic (e.g., amygdala) and paralimbic cortical areas (e.g., orbitofrontal cortex), whereas the matrix receives input from other prefrontal cortical regions, such as dorsolateral prefrontal cortex.

Striatal Organization

The topography of DA projections interfaces with regional and subcellular localization of DA receptors (Figure 3), which have fivefold to 20-fold higher density in striatum compared with other regions (28,86,101–103,107–110). Postsynaptic D_1 and D_2 are segregated onto different subpopulations of projection neurons and expressed on striatal interneurons. Cholinergic interneurons express D_2-like receptors that mediate fast synaptic events and locally regulate DA release (104,111). Taken together, ultrastructural and electrophysiologic experiments indicate that D_2-like receptors are positioned preferentially to mediate DA effects on striatopallidal projection neurons and cholinergic interneurons (28,112). As with DA inputs, DA receptors and modulators of DA release show distinct patch-matrix distributions in AST and SMST: patches are richer in D_1 receptors, lack parvalbumin-expressing interneurons, and show a paucity of cholinergic innervation as indexed by acetylcholinesterase fiber staining (103). Adding to this complexity, neuromodulators differentially affect DA release and projection neuron activity across the patch-matrix organization; for example, substance P facilitates DA release within the patch center, decreases it at the patch-matrix border, and has no effect in the matrix, whereas enkephalin selectively boosts patch projection output via delta opioid–mediated disinhibitory mechanisms (113,114).

Extrastriatal Organization

Extrastriatal regions including cortex are innervated predominantly by the dorsal tier DA system (Figure 2), which is poor in transporter and D_2 autoreceptors (101–103). In contrast to low innervation densities in rodents, primates have a dense and extensive cortical DA innervation (115). However, sparse cortical DAT expression suggests a low incidence of DA release sites (106). Moreover, low D_2 density and heterogeneous synaptology and DA receptor topography (28) all are consistent with the smaller PET DA release signal in extrastriatal regions. In cortex, D_2 are evenly distributed across projection neurons and fast-spiking interneurons (28,116). Thus, tracer displacement at D_2 on fast-spiking interneurons may contribute more to the PET DA release signal in the cortex than in the striatum. Spatiotemporal regulation of DA release and localization of D_2-like receptors varies considerably across regions and adds complexity to the interpretation of regional and disease-related variation in the PET DA release signal (Figure 3).

DISCUSSION

The literature reviewed here shows that 1) stimulant-induced presynaptic DA release is decreased in most brain regions in SZ (16), with the exception of the striatum where it is enhanced, especially in the rostral caudate (59); 2) in this region, the excess is not observed under conditions of substance abuse despite psychosis (11,82); 3) alterations in expression levels of receptors and transporters are less reliably observed (51,88), which does not exclude an alteration in function of these receptors in SZ because even under conditions of low DA tone, as in comorbidity with addiction, blocking striatal D_2 remains therapeutic, and stimulating striatal D_2 is psychotogenic (82); 4) antipsychotic exposure results in upregulation of striatal D_2 (51) and may induce downregulation, or normalization, of cortical D_1 (75); and 5) the global nature of the presynaptic DA dysregulation is likely to massively alter information processing in multiple domains and result in the global symptoms that we observe in SZ, although the specific mechanisms that mediate the formation of abnormal learning (117) and symptoms are currently unknown.

It remains to be seen whether extrastriatal DA deficits occur in the same subjects who display striatal DA upregulation, yielding a “dual dysregulation” of DA alteration, as proposed in the reformulation of the DA hypothesis of SZ (5,6). From this perspective, studies using stimulant challenge and studies using [^{18}F]DOPA have provided convergent results in striatum but not in extrastriatal regions. However, when investigators included metabolism of [^{18}F]6-FDA (k_{loss}) (46) in their model, they observed higher k_{loss} in the amygdala and midbrain in SZ, indicating a possible state of lower intracellular DA tone; excessive washout of DA is consistent with the lower evoked release that we observed. This provides one potential mechanism to reconcile these findings and to support our observation of extrastriatal DA release deficits. The finding of increased K_i^{cer} (91) is potentially susceptible to group differences in cerebellar concentration of [^{18}F]DOPA. Additional support to our finding of cortical and midbrain deficit derives from the postmortem observations of reduced tyrosine hydroxylase (118,119); however, high tyrosine hydroxylase (91) and high (120) or normal (121) tyrosine hydroxylase messenger RNA have also been reported. More research is needed to understand these discrepancies.

Because one of the main findings in SZ is dysregulation of presynaptic DA function, we have reviewed the multifactorial regulation of DA release and its detection with PET. The AST is of particular interest. In HC subjects, the PET DA release signal in the AST is lower than in the SMST (9,14,59), whereas in patients with SZ, it is increased to levels similar to the SMST. We speculate that in the healthy brain, subregional differences may reflect differences in DA innervation, regulation of DA release, or distributions of perisynaptic D_2-like receptors. The difference in the patch-to-matrix ratio between the AST and SMST could also reflect and/or contribute to lower spontaneous DA release in AST (104,122,123). For example, given the low cholinergic innervation of patches, acetylcholine augmentation of DA release may be lower in this compartment and relatively lower in the patch-enriched AST. We could postulate that, in SZ, a disruption of brain development leads to abnormal or incomplete development of the AST, consistent with structural imaging studies showing lower caudate volume in early-stage, unmedicated patients with SZ relative to HC subjects (103,124). A developmental disruption leading to altered differentiation of AST from SMST and/or lower patch/matrix compartmentalization in the AST might lead to abnormalities in the patterning of DA and other inputs to the AST, DA interactions with acetylcholine and other striatal neurotransmitters (103,104), and DA modulation of cortical inputs to the AST (125). Testing these ideas requires updating the existing postmortem literature (124) with studies applying modern labeling and imaging methods to render the three-dimensional chemoarchitecture of the striatal complex in healthy humans and patients with SZ. Additional models that consider regional and subregional variation in DA synaptology and modulation of DA release across striatal subcompartments are also needed.

The mechanisms underlying cortical deficits in the PET DA release signal in SZ remain to be determined, but given the distribution of D_2 receptors, they may involve changes in DA signaling at a variety of neuronal populations including cortical interneurons. The generalized and profound deficits in extrastriatal DA release raise an important therapeutic challenge for the field, as currently approved antipsychotics do not remedy this deficit or the resultant low stimulation of extrastriatal dopaminergic receptors. This generalized deficit is also consistent with the multidomain functional manifestations of the illness, ranging from deficits in social cognition to deficits in executive function and motivation. Although higher DA may be linked to better cognition in a brain without SZ (126–129), in SZ, higher DA may have a dysfunctional impact either because of its modulatory role on an already abnormal circuitry or because of intrinsic aberrant dynamics of DA cell firing patterns.

CONCLUSIONS

Although this literature does not provide mechanistic understanding of the dysfunction, it has provided a refined topographical knowledge that can be used in translational studies

and in drug development. Knowledge is limited at this point regarding the specific alterations in the multiple cellular components that could mediate the altered PET DA signal in SZ. We have reviewed and discussed a few "suspect" cellular mechanisms. These need to be formally tested in postmortem tissue, in animal models that show DA dysregulation, and in cellular systems such as induced pluripotent stem cells from patients who show abnormal DA PET signal to isolate specific components that may be involved. Once those components are defined, they can be used in drug development as specific targets for novel therapies. Our review highlights the urgent need for this cellular work to be carried out in tandem with imaging in patients.

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