Pathway-Specific Dopamine Abnormalities in Schizophrenia

Article *in* Biological psychiatry · March 2016

DOI: 10.1016/j.biopsych.2016.03.2104

6 authors, including:

Jodi J Weinstein
Columbia University
16 PUBLICATIONS **59** CITATIONS
SEE PROFILE

Muhammad O Chohan
Columbia University
5 PUBLICATIONS **117** CITATIONS
SEE PROFILE

Mark Slifstein
Stony Brook University Hospital
153 PUBLICATIONS **7,595** CITATIONS
SEE PROFILE

Lawrence S Kegeles
Columbia University
149 PUBLICATIONS **7,410** CITATIONS
SEE PROFILE

Review

Biological Psychiatry

Pathway-Specific Dopamine Abnormalities in Schizophrenia

Jodi J. Weinstein, Muhammad O. Chohan, Mark Slifstein, Lawrence S. Kegeles, Holly Moore, and Anissa Abi-Dargham

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

http://dx.doi.org/10.1016/j.biopsych.2016.03.2104

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

ISSN: 0006-3223

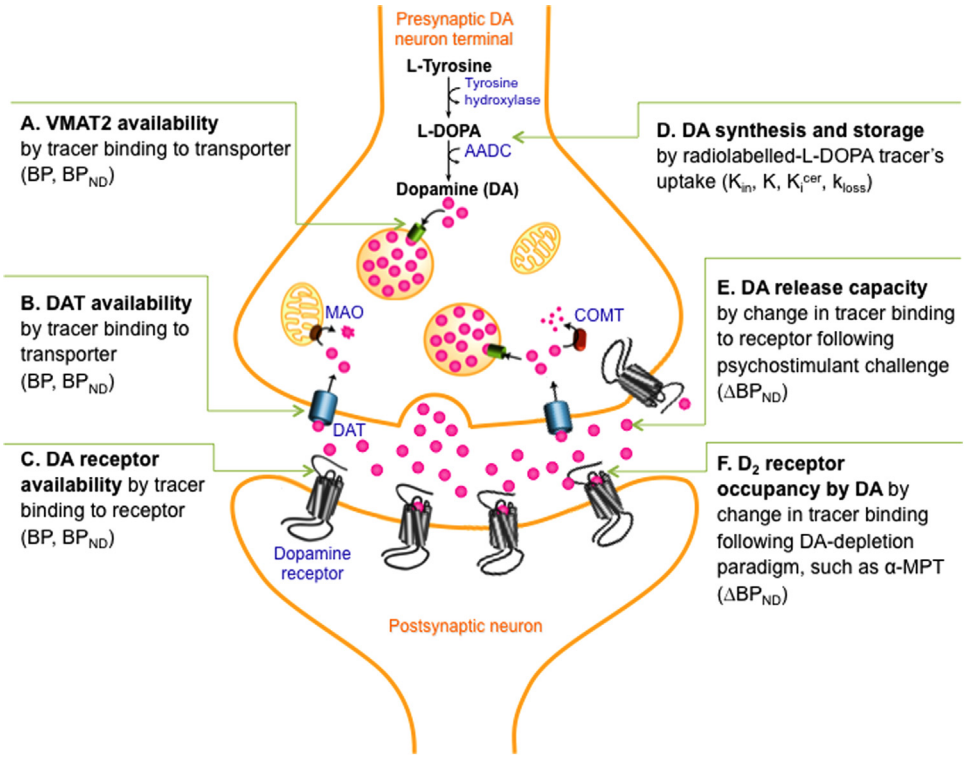

Figure 1. Dopaminergic imaging targets. Schematic of imaging methods used to measure aspects of the dopamine system in vivo. Graphic depicts progression of dopamine from synthesis **(D)**, storage **(A)**, to release **(E, F)**, then either reuptake by dopamine transporter **(B)** or binding to receptor **(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 non-displaceable 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

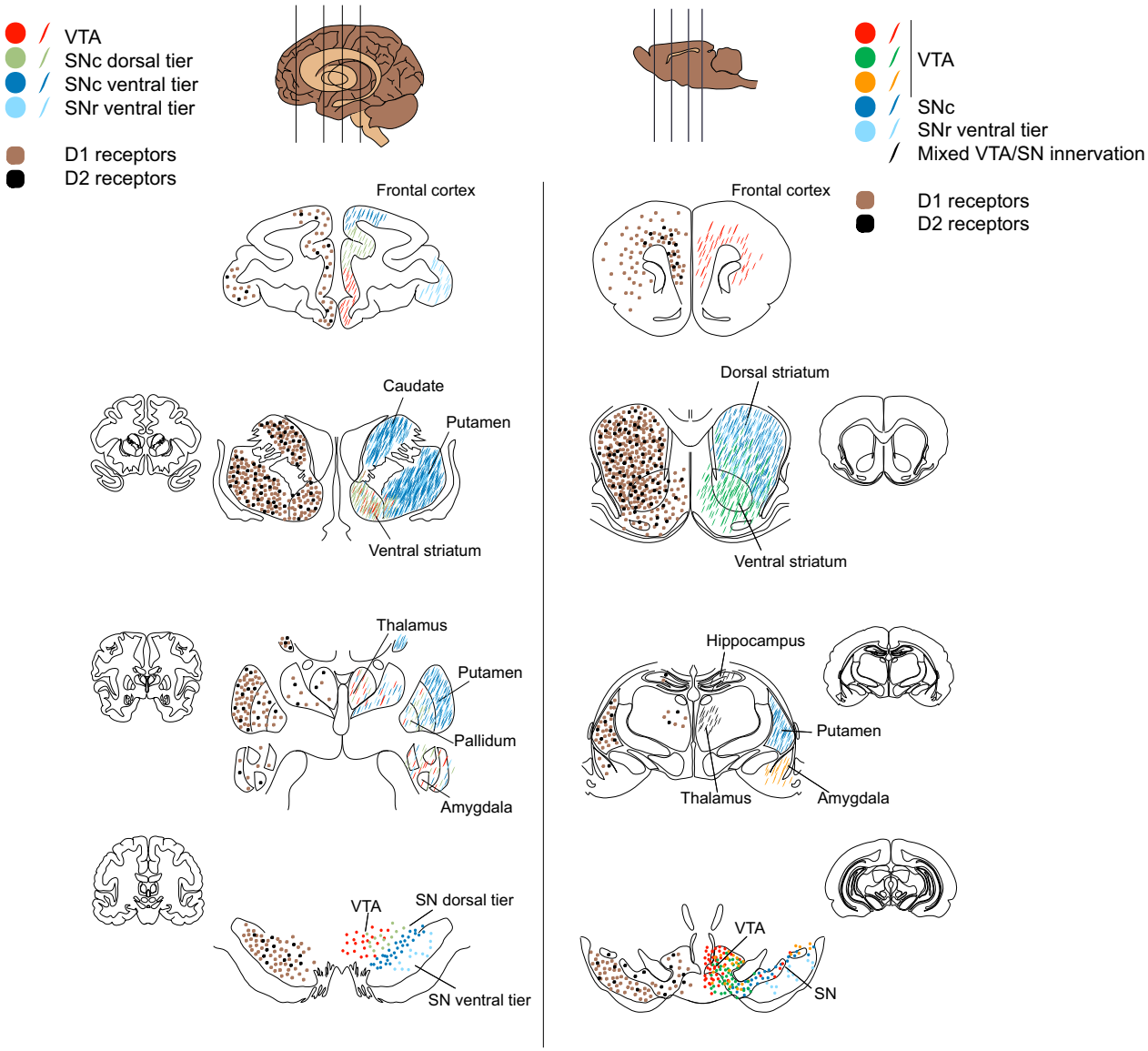

Figure 2. Topography of dopaminergic innervation and receptor distribution. Schematic representation of distributions of dopamine (DA) D_1 and D_2 receptors (left hemispheres) and patterns of dopaminergic innervations (right hemispheres) in select primate (left panel) and rodent (right panel) brain regions. *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

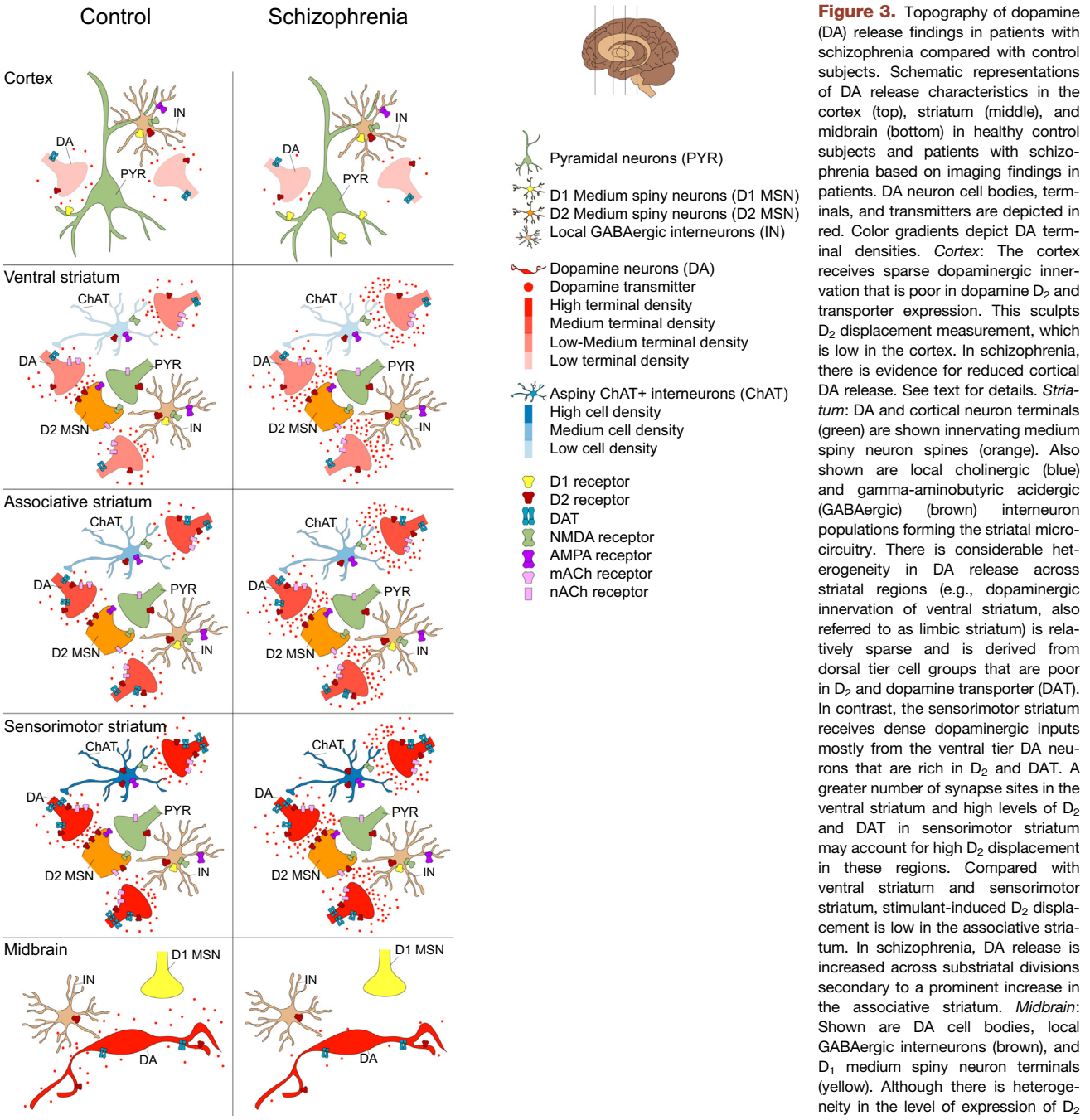

Figure 3. Topography of dopamine (DA) release findings in patients with schizophrenia compared with control subjects. Schematic representations of DA release characteristics in the cortex (top), striatum (middle), and midbrain (bottom) in healthy control subjects and patients with schizophrenia based 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

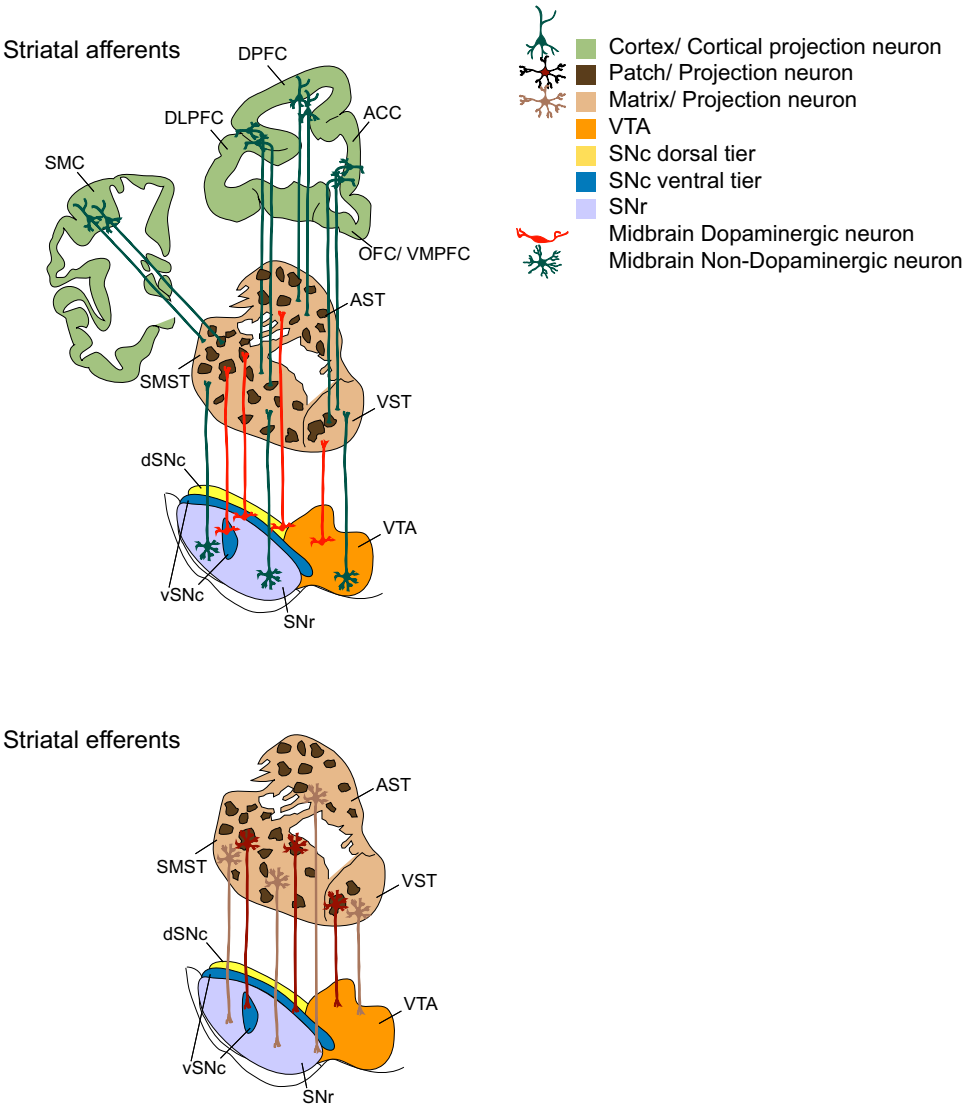

Figure 4. Striatal patch-matrix connectome. Schematic representation of striatal patch-matrix connectome. *Afferents*: The cortex topographically projects to the striatum. Within the cortex, deeper cortical layers innervate striatal patches (dark brown), whereas the surrounding matrix (light brown) is 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.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by the National Institute of Mental Health Sylvio O. Conte Center for the Study of Dopamine Dysfunction in Schizophrenia Grant No. P50 MH086404 (to AA-D, MS, and LSK; core 4 to MOC and HM) and Training in Schizophrenia and Psychotic Disorders: From Animal Models to Patients Grant No. T32 MH018870 (to JJW) and the Sidney R. Baer, Jr. Fund (to HM).

We thank Dr. Xiaoyan Xu for her assistance.

LSK has received research support from Amgen. MS has received research support from Forest Laboratories, Pierre Fabre, CHDI Foundation, and Otsuka and has provided consultation for Amgen. AA-D has received research support from Takeda and Forest Laboratories and has served on advisory boards for Roche, Forum Pharmaceuticals, and Otsuka. HM, MOC, and JJW report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Department of Psychiatry (JJW, MS, LSK, HM, AA-D), Columbia University, New York; and Divisions of Translational Imaging (JJW, MS, LSK, AA-D) and Integrative Neuroscience (MOC, HM), New York State Psychiatric Institute, New York, New York.

Address correspondence to Jodi J. Weinstein, M.D., New York State Psychiatric Institute, 1051 Riverside Drive, Unit 31, New York, NY 10032; E-mail: jodi.j.weinstein@aya.yale.edu.

Received Oct 27, 2015; revised Mar 21, 2016; accepted Mar 25, 2016.

Supplementary material cited in this article is available online at http://dx.doi.org/10.1016/j.biopsych.2016.03.2104.

REFERENCES

1. Rossum V (1966): The significance of dopamine receptor blockade for the mechanism of action of neuroleptic drugs. Arch Int Pharmacodyn Ther 160:492–494.
2. Carlsson A (1978): Antipsychotic drugs, neurotransmitters, and schizophrenia. Am J Psychiatry 135:165–173.
3. Seeman P, Lee T, Chau-Wong M, Wong K (1976): Antipsychotic drug doses and neuroleptic/dopamine receptors. Nature 261: 717–719.
4. Lieberman JA, Kane JM, Alvir J (1987): Provocative tests with psychostimulant drugs in schizophrenia. Psychopharmacology 91: 415–433.
5. Weinberger DR, Berman KF (1988): Speculation on the meaning of cerebral metabolic hypofrontality in schizophrenia. Schizophr Bull 14:157–168.
6. Davis KL, Kahn RS, Ko G, Davidson M (1991): Dopamine in schizophrenia: a review and reconceptualization. Am J Psychiatry 148:1474–1486.
7. Yung AR, McGorry PD, McFarlane CA, Jackson HJ, Patton GC, Rakkar A (1996): Monitoring and care of young people at incipient risk of psychosis. Schizophr Bull 22:283–303.
8. Yung AR, Phillips LJ, McGorry PD, McFarlane CA, Francey S, Harrigan S, *et al*. (1998): Prediction of psychosis. A step towards indicated prevention of schizophrenia. Br J Psychiatry Suppl 172:14–20.
9. Howes OD, Montgomery AJ, Asselin MC, Murray RM, Valli I, Tabraham P, *et al*. (2009): Elevated striatal dopamine function linked to prodromal signs of schizophrenia. Arch Gen Psychiatry 66:13–20.
10. Suridjan I, Rusjan P, Addington J, Wilson AA, Houle S, Mizrahi R (2013): Dopamine D2 and D3 binding in people at clinical high risk for schizophrenia, antipsychotic-naive patients and healthy controls while performing a cognitive task. J Psychiatry Neurosci 38:98–106.
11. Mizrahi R, Kenk M, Suridjan I, Boileau I, George TP, McKenzie K, *et al*. (2014): Stress-induced dopamine response in subjects at clinical high risk for schizophrenia with and without concurrent cannabis use. Neuropsychopharmacology 39:1479–1489.
12. Adler CM, Elman I, Weisenfeld N, Kestler L, Pickar D, Breier A (2000): Effects of acute metabolic stress on striatal dopamine release in healthy volunteers. Neuropsychopharmacology 22:545–550.
13. Pruessner JC, Champagne F, Meaney MJ, Dagher A (2004): Dopamine release in response to a psychological stress in humans and its relationship to early life maternal care: A positron emission tomography study using [11C]raclopride. J Neurosci 24:2825–2831.
14. Mizrahi R, Addington J, Rusjan PM, Suridjan I, Ng A, Boileau I, *et al*. (2012): Increased stress-induced dopamine release in psychosis. Biol Psychiatry 71:561–567.
15. Soliman A, O'Driscoll GA, Pruessner J, Holahan AL, Boileau I, Gagnon D, *et al*. (2008): Stress-induced dopamine release in humans at risk of psychosis: A [11C]raclopride PET study. Neuropsychopharmacology 33:2033–2041.
16. Slifstein M, van de Giessen E, Van Snellenberg J, Thompson JL, Narendran R, Gil R, *et al*. (2015): Deficits in prefrontal cortical and extrastriatal dopamine release in schizophrenia: A positron emission tomographic functional magnetic resonance imaging study. JAMA. Psychiatry 72:316–324.
17. Innis RB, Cunningham VJ, Delforge J, Fujita M, Gjedde A, Gunn RN, *et al*. (2007): Consensus nomenclature for in vivo imaging of reversibly binding radioligands. J Cereb Blood Flow Metab 27: 1533–1539.
18. Slifstein M, Laruelle M (2001): Models and methods for derivation of in vivo neuroreceptor parameters with PET and SPECT reversible radiotracers. Nucl Med Biol 28:595–608.
19. Slifstein M, Hwang D-R, Huang Y, Guo N, Sudo Y, Narendran R, *et al*. (2004): In vivo affinity of [18F]fallypride for striatal and extrastriatal dopamine D2 receptors in nonhuman primates. Psychopharmacology 175:274–286.
20. Mukherjee J, Yang ZY, Das MK, Brown T (1995): Fluorinated benzamide neuroleptics—III. development of (S)-N-[(1-allyl-2-pyrrolidinyl)methyl]-5-(3-[18F]fluoropropyl)-2, 3-dimethoxybenzamide as an improved dopamine D-2 receptor tracer. Nucl Med Biol 22: 283–296.
21. Halldin C, Farde L, Hogberg T, Mohell N, Hall H, Suhara T, *et al*. (1995): Carbon-11-FLB 457: A radioligand for extrastriatal D2 dopamine receptors. J Nucl Med 36:1275–1281.
22. Kessler RM, Mason NS, Votaw JR, De Paulis T, Clanton JA, Ansari MS, *et al*. (1992): Visualization of extrastriatal dopamine D2 receptors in the human brain. Eur J Pharmacol 223:105–107.
23. Narendran R, Slifstein M, Guillin O, Hwang YY, Hwang DR, Scher E, *et al*. (2006): The dopamine (D-2/3) receptor agonist positron emission tomography radiotracer [C-11)-(+)-PHNO is a D-3 receptor preferring agonist in vivo. Synapse 60:485–495.
24. Rabiner E, Slifstein M, Nobrega J, Plisson C, Huiban M, Raymond R, *et al*. (2009): In vivo quantification of regional dopamine-D3 receptor binding potential of (+)PHNO: Studies in non-hman primates and transgenic mice. Synapse 63:782–793.
25. Wilson AA, McCormick P, Kapur S, Willeit M, Garcia A, Hussey D, *et al*. (2005): Radiosynthesis and evaluation of [11C]-(+)-4-propyl-3,4,4a,5,6,10b-hexahydro-2H-naphtho[1,2-b][1,4]oxazin-9-ol as a potential radiotracer for in vivo imaging of the dopamine D2 high-affinity state with positron emission tomography. J Med Chem 48: 4153–4160.

26. Abi-Dargham A, Martinez D, Mawlawi O, Simpson N, Hwang DR, Slifstein M, *et al*. (2000): Measurement of striatal and extrastriatal dopamine D1 receptor binding potential with [11C]NNC 112 in humans: Validation and reproducibility. J Cereb Blood Flow Metab 20:225–243.
27. Okubo Y, Suhara T, Suzuki K, Kobayashi K, Inoue O, Terasaki O, *et al*. (1997): Decreased prefrontal dopamine D1 receptors in schizophrenia revealed by PET. Nature 385:634–636.
28. Sesack SR (2002): Synaptology of dopamine neurons. In: Di Chiara G, editor. Dopamine in the CNS. Berlin: Springer-Verlag, 63–120.
29. Egerton A, Mehta MA, Montgomery AJ, Lappin JM, Howes OD, Reeves SJ, *et al*. (2009): The dopaminergic basis of human behaviors: A review of molecular imaging studies. Neurosci Biobehav Rev 33:1109–1132.
30. Sesack SR, Aoki C, Pickel VM (1994): Ultrastructural localization of D2 receptor-like immunoreactivity in midbrain dopamine neurons and their striatal targets. J Neurosci 14:88–106.
31. Hersch SM, Ciliax BJ, Gutekunst CA, Rees HD, Heilman CJ, Yung KK, *et al*. (1995): Electron microscopic analysis of D1 and D2 dopamine receptor proteins in the dorsal striatum and their synaptic relationships with motor corticostriatal afferents. J Neurosci 15: 5222–5237.
32. Yung KK, Bolam JP, Smith AD, Hersch SM, Ciliax BJ, Levey AI (1995): Immunocytochemical localization of D1 and D2 dopamine receptors in the basal ganglia of the rat: Light and electron microscopy. Neuroscience 65:709–730.
33. Laruelle M (2000): Imaging synaptic neurotransmission with in vivo binding competition techniques: A critical review. J Cereb Blood Flow Metab 20:423–451.
34. Cumming P, Gjedde A (1998): Compartmental analysis of dopa decarboxylation in living brain from dynamic positron emission tomograms. Synapse 29:37–61.
35. Kumakura Y, Vernaleken I, Grunder G, Bartenstein P, Gjedde A, Cumming P (2005): PET studies of net blood-brain clearance of FDOPA to human brain: Age-dependent decline of [18F]fluorodopamine storage capacity. J Cereb Blood Flow Metab 25: 807–819.
36. Sossi V, Doudet D, Holden J (2001): A reversible tracer analysis approach to the study of effective dopamine turnover. J Cereb Blood Flow Metab 21:469–476.
37. Cropley VL, Fujita M, Bara-Jimenez W, Brown AK, Zhang XY, Sangare J, *et al*. (2008): Pre- and post-synaptic dopamine imaging and its relation with frontostriatal cognitive function in Parkinson disease: PET studies with [11C]NNC 112 and [18F]FDOPA. Psychiatry Res 163:171–182.
38. Kish SJ, Robitaille Y, el-Awar M, Clark B, Schut L, Ball MJ, *et al*. (1992): Striatal monoamine neurotransmitters and metabolites in dominantly inherited olivopontocerebellar atrophy. Neurology 42: 1573–1577.
39. Laruelle M, Wallace E, Seibyl JP, Baldwin RM, Zea-Ponce Y, Zoghbi SS, *et al*. (1994): Graphical, kinetic and equilibrium analysis of [123-I] b-CIT in vivo binding to dopamine transporters in healthy subjects. J Cereb Blood Flow Metab 14:982–994.
40. Reith J, Benkelfat C, Sherwin A, Yasuhara Y, Kuwabara H, Andermann F, *et al*. (1994): Elevated dopa decarboxylase activity in living brain of patients with psychosis. Proc Natl Acad Sci U S A 91: 11651–11654.
41. Hietala J, Syvalahti E, Vuorio K, Rakkolainen V, Bergman J, Haaparanta M, *et al*. (1995): Presynaptic dopamine function in striatum of neuroleptic-naive schizophrenic patients. Lancet 346: 1130–1131.
42. Hietala J, Syvalahti E, Vilkman H, Vuorio K, Rakkolainen V, Bergman J, *et al*. (1999): Depressive symptoms and presynaptic dopamine function in neuroleptic-naive schizophrenia. Schizophr Res 35: 41–50.
43. Meyer-Lindenberg A, Miletich RS, Kohn PD, Esposito G, Carson RE, Quarantelli M, *et al*. (2002): Reduced prefrontal activity predicts exaggerated striatal dopaminergic function in schizophrenia. Nat Neurosci 5:267–271.
44. McGowan S, Lawrence AD, Sales T, Quested D, Grasby P (2004): Presynaptic dopaminergic dysfunction in schizophrenia: A positron emission tomographic [18F]fluorodopa study. Arch Gen Psychiatry 61:134–142.
45. Lindstrom LH, Gefvert O, Hagberg G, Lundberg T, Bergstrom M, Hartvig P, *et al*. (1999): Increased dopamine synthesis rate in medial prefrontal cortex and striatum in schizophrenia indicated by L-(beta-11C) DOPA and PET. Biol Psychiatry 46:681–688.
46. Kumakura Y, Cumming P, Vernaleken I, Buchholz HG, Siessmeier T, Heinz A, *et al*. (2007): Elevated [18F]fluorodopamine turnover in brain of patients with schizophrenia: An [18F]fluorodopa/positron emission tomography study. J Neurosci 27:8080–8087.
47. Nozaki S, Kato M, Takano H, Ito H, Takahashi H, Arakawa R, *et al*. (2009): Regional dopamine synthesis in patients with schizophrenia using L-[beta-11C]DOPA PET. Schizophr Res 108:78–84.
48. Elkashef AM, Doudet D, Bryant T, Cohen RM, Li SH, Wyatt RJ (2000): 6-(18)F-DOPA PET study in patients with schizophrenia. Positron emission tomography. Psychiatry Res 100:1–11.
49. Dao-Castellana MH, Paillere-Martinot ML, Hantraye P, Attar-Levy D, Remy P, Crouzel C, *et al*. (1997): Presynaptic dopaminergic function in the striatum of schizophrenic patients. Schizophr Res 23:167–174.
50. Fusar-Poli P, Meyer-Lindenberg A (2013): Striatal presynaptic dopamine in schizophrenia, part II: Meta-analysis of [(18)F/(11)C]-DOPA PET studies. Schizophr Bull 39:33–42.
51. Howes OD, Kambeitz J, Kim E, Stahl D, Slifstein M, Abi-Dargham A, *et al*. (2012): The nature of dopamine dysfunction in schizophrenia and what this means for treatment. Arch Gen Psychiatry 69: 776–786.
52. Laruelle M, Abi-Dargham A, van Dyck CH, Gil R, D'Souza CD, Erdos J, *et al*. (1996): Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects. Proc Natl Acad Sci U S A 93: 9235–9240.
53. Abi-Dargham A, Gil R, Krystal J, Baldwin RM, Seibyl JP, Bowers M, *et al*. (1998): Increased striatal dopamine transmission in schizophrenia: Confirmation in a second cohort. Am J Psychiatry 155: 761–767.
54. Pogarell O, Koch W, Karch S, Dehning S, Muller N, Tatsch K, *et al*. (2012): Dopaminergic neurotransmission in patients with schizophrenia in relation to positive and negative symptoms. Pharmacopsychiatry 45(suppl 1):S36–S41.
55. Breier A, Su TP, Saunders R, Carson RE, Kolachana BS, de Bartolomeis A, *et al*. (1997): Schizophrenia is associated with elevated amphetamine-induced synaptic dopamine concentrations: Evidence from a novel positron emission tomography method. Proc Natl Acad Sci U S A 94:2569–2574.
56. Laruelle M, Abi-Dargham A, Gil R, Kegeles L, Innis R (1999): Increased dopamine transmission in schizophrenia: Relationship to illness phases. Biol Psychiatry 46:56–72.
57. Abi-Dargham A, Rodenhiser J, Printz D, Zea-Ponce Y, Gil R, Kegeles LS, *et al*. (2000): Increased baseline occupancy of D2 receptors by dopamine in schizophrenia. Proc Natl Acad Sci U S A 97:8104–8109.
58. Abi-Dargham A, van de Giessen E, Slifstein M, Kegeles LS, Laruelle M (2009): Baseline and amphetamine-stimulated dopamine activity are related in drug-naive schizophrenic subjects. Biol Psychiatry 65: 1091–1093.
59. Kegeles LS, Abi-Dargham A, Frankle WG, Gil R, Cooper TB, Slifstein M, *et al*. (2010): Increased synaptic dopamine function in associative regions of the striatum in schizophrenia. Arch Gen Psychiatry 67: 231–239.
60. Hitri A, Casanova MF, Kleinman JE, Weinberger DR, Wyatt RJ (1995): Age-related changes in [3H]GBR 12935 binding site density in the prefrontal cortex of controls and schizophrenics. Biol Psychiatry 37:175–182.
61. Taylor SF, Koeppe RA, Tandon R, Zubieta JK, Frey KA (2000): In vivo measurement of the vesicular monoamine transporter in schizophrenia. Neuropsychopharmacology 23:667–675.
62. Laakso A, Vilkman H, Alakare B, Haaparanta M, Bergman J, Solin O, *et al*. (2000): Striatal dopamine transporter binding in neuroleptic-

naive patients with schizophrenia studied with positron emission tomography. Am J Psychiatry 157:269–271.
63. Laruelle M, Abi-Dargham A, van Dyck C, Gil R, D'Souza DC, Krystal J, *et al*. (2000): Dopamine and serotonin transporters in patients with schizophrenia: An imaging study with [(123)I]beta-CIT. Biol Psychiatry 47:371–379.
64. Laakso A, Bergman J, Haaparanta M, Vilkman H, Solin O, Syvalahti E, *et al*. (2001): Decreased striatal dopamine transporter binding in vivo in chronic schizophrenia. Schizophr Res 52:115–120.
65. Lavalaye J, Linszen DH, Booij J, Dingemans PM, Reneman L, Habraken JB, *et al*. (2001): Dopamine transporter density in young patients with schizophrenia assessed with [123]FP-CIT SPECT. Schizophr Res 47:59–67.
66. Hsiao MC, Lin KJ, Liu CY, Tzen KY, Yen TC (2003): Dopamine transporter change in drug-naive schizophrenia: An imaging study with 99mTc-TRODAT-1. Schizophr Res 65:39–46.
67. Schmitt GJ, la Fougere C, Dresel S, Frodl T, Hahn K, Moller HJ, *et al*. (2008): Dual-isotope SPECT imaging of striatal dopamine: First episode, drug naive schizophrenic patients. Schizophr Res 101: 133–141.
68. Mateos JJ, Lomena F, Parellada E, Mireia F, Fernandez-Egea E, Pavia J, *et al*. (2007): Lower striatal dopamine transporter binding in neuroleptic-naive schizophrenic patients is not related to antipsychotic treatment but it suggests an illness trait. Psychopharmacology 191:805–811.
69. Mateos JJ, Lomena F, Parellada E, Font M, Fernandez E, Pavia J, *et al*. (2005): Decreased striatal dopamine transporter binding assessed with [123I] FP-CIT in first-episode schizophrenic patients with and without short-term antipsychotic-induced parkinsonism. Psychopharmacology 181:401–406.
70. Yoder KK, Hutchins GD, Morris ED, Brashear A, Wang C, Shekhar A (2004): Dopamine transporter density in schizophrenic subjects with and without tardive dyskinesia. Schizophr Res 71:371–375.
71. Yang YK, Yu L, Yeh TL, Chiu NT, Chen PS, Lee IH, *et al*. (2004): Associated alterations of striatal dopamine D2/D3 receptor and transporter binding in drug-naive patients with schizophrenia: A dual-isotope SPECT study. Am J Psychiatry 161:1496–1498.
72. Arakawa R, Ichimiya T, Ito H, Takano A, Okumura M, Takahashi H, *et al*. (2009): Increase in thalamic binding of [(11)C]PE2I in patients with schizophrenia: A positron emission tomography study of dopamine transporter. J Psychiatr Res 43:1219–1223.
73. Karlsson P, Farde L, Halldin C, Sedvall G (2002): P.E.T. study of D(1) dopamine receptor binding in neuroleptic-naive patients with schizophrenia. Am J Psychiatry 159:761–767.
74. Abi-Dargham A, Mawlawi O, Lombardo I, Gil R, Martinez D, Huang Y, *et al*. (2002): Prefrontal dopamine D1 receptors and working memory in schizophrenia. J Neurosci 22:3708–3719.
75. Abi-Dargham A, Xu X, Thompson JL, Gil R, Kegeles LS, Urban N, *et al*. (2012): Increased prefrontal cortical D1 receptors in drug naive patients with schizophrenia: A PET study with [11C]NNC112. J Psychopharmacol 26:794–805.
76. Howes OD, Bose SK, Turkheimer F, Valli I, Egerton A, Valmaggia LR, *et al*. (2011): Dopamine synthesis capacity before onset of psychosis: A prospective [18F]-DOPA PET imaging study. Am J Psychiatry 168:1311–1317.
77. Fusar-Poli P, Howes OD, Allen P, Broome M, Valli I, Asselin MC, *et al*. (2010): Abnormal frontostriatal interactions in people with prodromal signs of psychosis: a multimodal imaging study. Arch Gen Psychiatry 67:683–691.
78. Fusar-Poli P, Howes OD, Allen P, Broome M, Valli I, Asselin MC, *et al*. (2011): Abnormal prefrontal activation directly related to presynaptic striatal dopamine dysfunction in people at clinical high risk for psychosis. Mol Psychiatry 16:67–75.
79. Howes O, Bose S, Turkheimer F, Valli I, Egerton A, Stahl D, *et al*. (2011): Progressive increase in striatal dopamine synthesis capacity as patients develop psychosis: A PET study. Mol Psychiatry 16: 885–886.
80. Egerton A, Chaddock CA, Winton-Brown TT, Bloomfield MA, Bhattacharyya S, Allen P, *et al*. (2013): Presynaptic striatal dopamine dysfunction in people at ultra-high risk for psychosis: Findings in a second cohort. Biol Psychiatry 74:106–112.
81. Demjaha A, Murray RM, McGuire PK, Kapur S, Howes OD (2012): Dopamine synthesis capacity in patients with treatment-resistant schizophrenia. Am J Psychiatry 169:1203–1210.
82. Thompson JL, Urban N, Slifstein M, Xu X, Kegeles LS, Girgis RR, *et al*. (2013): Striatal dopamine release in schizophrenia comorbid with substance dependence. Mol Psychiatry 18:909–915.
83. Talvik M, Nordstrom AL, Olsson H, Halldin C, Farde L (2003): Decreased thalamic D2/D3 receptor binding in drug-naive patients with schizophrenia: A PET study with [11C]FLB 457. Int J Neuropsychopharmacol 6:361–370.
84. Suhara T, Okubo Y, Yasuno F, Sudo Y, Inoue M, Ichimiya T, *et al*. (2002): Decreased dopamine D2 receptor binding in the anterior cingulate cortex in schizophrenia. Arch Gen Psychiatry 59:25–30.
85. Glenthoj BY, Mackeprang T, Svarer C, Rasmussen H, Pinborg LH, Friberg L, *et al*. (2006): Frontal dopamine D(2/3) receptor binding in drug-naive first-episode schizophrenic patients correlates with positive psychotic symptoms and gender. Biol Psychiatry 60: 621–629.
86. Kegeles LS, Slifstein M, Xu X, Urban N, Thompson JL, Moadel T, *et al*. (2010): Striatal and extrastriatal dopamine D2/D3 receptors in schizophrenia evaluated with [18F]fallypride positron emission tomography. Biol Psychiatry 68:634–641.
87. Kessler RM, Woodward ND, Riccardi P, Li R, Ansari MS, Anderson S, *et al*. (2009): Dopamine D2 receptor levels in striatum, thalamus, substantia nigra, limbic regions, and cortex in schizophrenic subjects. Biol Psychiatry 65:1024–1031.
88. Kambeitz J, Abi-Dargham A, Kapur S, Howes OD (2014): Alterations in cortical and extrastriatal subcortical dopamine function in schizophrenia: Systematic review and meta-analysis of imaging studies. Br J Psychiatry 204:420–429.
89. Kosaka J, Takahashi H, Ito H, Takano A, Fujimura Y, Matsumoto R, *et al*. (2010): Decreased binding of [11C]NNC112 and [11C] SCH23390 in patients with chronic schizophrenia. Life Sci 86: 814–818.
90. Poels EM, Girgis RR, Thompson JL, Slifstein M, Abi-Dargham A (2013): In vivo binding of the dopamine-1 receptor PET tracers [11C] NNC112 and [11C]SCH23390: A comparison study in individuals with schizophrenia. Psychopharmacology 228:167–174.
91. Howes OD, Williams M, Ibrahim K, Leung G, Egerton A, McGuire PK, *et al*. (2013): Midbrain dopamine function in schizophrenia and depression: A post-mortem and positron emission tomographic imaging study. Brain 136:3242–3251.
92. Allen P, Luigjes J, Howes OD, Egerton A, Hirao K, Valli I, *et al*. (2012): Transition to psychosis associated with prefrontal and subcortical dysfunction in ultra high-risk individuals. Schizophr Bull 38:1268–1276.
93. Zubieta JK, Taylor SF, Huguelet P, Koeppe RA, Kilbourn MR, Frey KA (2001): Vesicular monoamine transporter concentrations in bipolar disorder type I, schizophrenia, and healthy subjects. Biol Psychiatry 49:110–116.
94. Lehrer DS, Christian BT, Kirbas C, Chiang M, Sidhu S, Short H, *et al*. (2010): 18F-fallypride binding potential in patients with schizophrenia compared to healthy controls. Schizophr Res 122:43–52.
95. Talvik M, Nordstrom AL, Okubo Y, Olsson H, Borg J, Halldin C, *et al*. (2006): Dopamine D2 receptor binding in drug-naive patients with schizophrenia examined with raclopride-C11 and positron emission tomography. Psychiatry Res 148:165–173.
96. Tuppurainen H, Kuikka JT, Laakso MP, Viinamaki H, Husso M, Tiihonen J (2006): Midbrain dopamine D2/3 receptor binding in schizophrenia. Eur Arch Psychiatry Clin Neurosci 256:382–387.
97. Graff-Guerrero A, Mizrahi R, Agid O, Marcon H, Barsoum P, Rusjan P, *et al*. (2009): The dopamine D2 receptors in high-affinity state and D3 receptors in schizophrenia: a clinical [11C]-(+)-PHNO PET study. Neuropsychopharmacology 34:1078–1086.
98. Buchsbaum MS, Christian BT, Lehrer DS, Narayanan TK, Shi B, Mantil J, *et al*. (2006): D2/D3 dopamine receptor binding with [F-18] fallypride in thalamus and cortex of patients with schizophrenia. Schizophr Res 85:232–244.

99. Yasuno F, Suhara T, Okubo Y, Sudo Y, Inoue M, Ichimiya T, *et al*. (2004): Low dopamine D(2) receptor binding in subregions of the thalamus in schizophrenia. Am J Psychiatry 161:1016–1022.
100. Martinez D, Slifstein M, Broft A, Mawlawi O, Hwang DR, Huang Y, *et al*. (2003): Imaging human mesolimbic dopamine transmission with positron emission tomography. Part II: Amphetamine-induced dopamine release in the functional subdivisions of the striatum. J Cereb Blood Flow Metabol 23:285–300.
101. Haber SN, Knutson B (2010): The reward circuit: Linking primate anatomy and human imaging. Neuropsychopharmacology 35:4–26.
102. Joel D, Weiner I (2000): The connections of the dopaminergic system with the striatum in rats and primates: An analysis with respect to the functional and compartmental organization of the striatum. Neuroscience 96:451–474.
103. Bentivoglio M, Morelli M (2005): The organization and circuits of mesencephalic dopaminergic neurons and the distribution of dopamine receptors in the brain. Handbook of Chemical Neuroanatomy 21:1–107.
104. Rice ME, Patel JC, Cragg SJ (2011): Dopamine release in the basal ganglia. Neuroscience 198:112–137.
105. Lammel S, Hetzel A, Hackel O, Jones I, Liss B, Roeper J (2008): Unique properties of mesoprefrontal neurons within a dual mesocorticolimbic dopamine system. Neuron 57:760–773.
106. Haber SN, Ryoo H, Cox C, Lu W (1995): Subsets of midbrain dopaminergic neurons in monkeys are distinguished by different levels of mRNA for the dopamine transporter: Comparison with the mRNA for the D2 receptor, tyrosine hydroxylase and calbindin immunoreactivity. J Comp Neurol 362:400–410.
107. Cropley VL, Innis RB, Nathan PJ, Brown AK, Sangare JL, Lerner A, *et al*. (2008): Small effect of dopamine release and no effect of dopamine depletion on [18F]fallypride binding in healthy humans. Synapse 62:399–408.
108. Kegeles LS, Slifstein M, Frankle WG, Xu X, Hackett E, Bae SA, *et al*. (2008): Dose-occupancy study of striatal and extrastriatal dopamine D2 receptors by aripiprazole in schizophrenia with PET and [18F] fallypride. Neuropsychopharmacology 33:3111–3125.
109. Riccardi P, Baldwin R, Salomon R, Anderson S, Ansari MS, Li R, *et al*. (2008): Estimation of baseline dopamine D2 receptor occupancy in striatum and extrastriatal regions in humans with positron emission tomography with [18F] fallypride. Biol Psychiatry 63: 241–244.
110. Slifstein M, Kegeles LS, Xu X, Thompson JL, Urban N, Castrillon J, *et al*. (2010): Striatal and extrastriatal dopamine release measured with PET and [(18)F] fallypride. Synapse 64:350–362.
111. Chuhma N, Mingote S, Moore H, Rayport S (2014): Dopamine neurons control striatal cholinergic neurons via regionally heterogeneous dopamine and glutamate signaling. Neuron 81:901–912.
112. Gonzales KK, Smith Y (2015): Cholinergic interneurons in the dorsal and ventral striatum: Anatomical and functional considerations in normal and diseased conditions. Ann N Y Acad Sci 1349:1–45.
113. Banghart MR, Neufeld SQ, Wong NC, Sabatini BL (2015): Enkephalin disinhibits mu opioid receptor-rich striatal patches via delta opioid receptors. Neuron 88:1227–1239.
114. Brimblecombe KR, Cragg SJ (2015): Substance P weights striatal dopamine transmission differently within the striosome-matrix axis. J Neurosci 35:9017–9023.
115. Berger B, Gaspar P, Verney C (1991): Dopaminergic innervation of the cerebral cortex: Unexpected differences between rodents and primates. Trends Neurosci 14:21–27.
116. Tritsch NX, Sabatini BL (2012): Dopaminergic modulation of synaptic transmission in cortex and striatum. Neuron 76:33–50.
117. Schultz W (2002): Getting formal with dopamine and reward. Neuron 36:241–263.
118. Rice MW, Roberts RC, Melendez-Ferro M, Perez-Costas E (2016): Mapping dopaminergic deficiencies in the substantia nigra/ventral tegmental area in schizophrenia. Brain Struct Funct 221:185–201.
119. Akil M, Edgar CL, Pierri JN, Casali S, Lewis DA (2000): Decreased density of tyrosine hydroxylase-immunoreactive axons in the entorhinal cortex of schizophrenic subjects. Biol Psychiatry 47:361–370.
120. Mueller HT, Haroutunian V, Davis KL, Meador-Woodruff JH (2004): Expression of the ionotropic glutamate receptor subunits and NMDA receptor-associated intracellular proteins in the substantia nigra in schizophrenia. Brain Res Mol Brain Res 121:60–69.
121. Ichinose H, Ohye T, Fujita K, Pantucek F, Lange K, Riederer P, *et al*. (1994): Quantification of mRNA of tyrosine hydroxylase and aromatic L-amino acid decarboxylase in the substantia nigra in Parkinson's disease and schizophrenia. J Neural Transm Park Dis Dement Sect 8:149–158.
122. Kemel ML, Desban M, Glowinski J, Gauchy C (1989): Distinct presynaptic control of dopamine release in striosomal and matrix areas of the cat caudate nucleus. Proc Natl Acad Sci U S A 86:9006–9010.
123. Graybiel AM, Ragsdale CW Jr (1978): Histochemically distinct compartments in the striatum of human, monkeys, and cat demonstrated by acetylthiocholinesterase staining. Proc Natl Acad Sci U S A 75:5723–5726.
124. Perez-Costas E, Melendez-Ferro M, Roberts RC (2010): Basal ganglia pathology in schizophrenia: Dopamine connections and anomalies. J Neurochem 113:287–302.
125. Crittenden JR, Graybiel AM (2011): Basal ganglia disorders associated with imbalances in the striatal striosome and matrix compartments. Front Neuroanat 5:59.
126. Vernaleken I, Buchholz HG, Kumakura Y, Siessmeier T, Stoeter P, Bartenstein P, *et al*. (2007): "Prefrontal" cognitive performance of healthy subjects positively correlates with cerebral FDOPA influx: An exploratory [18F]-fluoro-L-DOPA-PET investigation. Hum Brain Mapp 28:931–939.
127. Cools R, Gibbs SE, Miyakawa A, Jagust W, D'Esposito M (2008): Working memory capacity predicts dopamine synthesis capacity in the human striatum. J Neurosci 28:1208–1212.
128. Cools R, Frank MJ, Gibbs SE, Miyakawa A, Jagust W, D'Esposito M (2009): Striatal dopamine predicts outcome-specific reversal learning and its sensitivity to dopaminergic drug administration. J Neurosci 29:1538–1543.
129. Deserno L, Huys QJ, Boehme R, Buchert R, Heinze HJ, Grace AA, *et al*. (2015): Ventral striatal dopamine reflects behavioral and neural signatures of model-based control during sequential decision making. Proc Natl Acad Sci U S A 112:1595–1600.