

# The Role of Genes, Stress, and Dopamine in the Development of Schizophrenia

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## ABSTRACT

The dopamine hypothesis is the longest standing pathoetiologic theory of schizophrenia. Because it was initially based on indirect evidence and findings in patients with established schizophrenia, it was unclear what role dopamine played in the onset of the disorder. However, recent studies in people at risk of schizophrenia have found elevated striatal dopamine synthesis capacity and increased dopamine release to stress. Furthermore, striatal dopamine changes have been linked to altered cortical function during cognitive tasks, in line with preclinical evidence that a circuit involving cortical projections to the striatum and midbrain may underlie the striatal dopamine changes. Other studies have shown that a number of environmental risk factors for schizophrenia, such as social isolation and childhood trauma, also affect presynaptic dopaminergic function. Advances in preclinical work and genetics have begun to unravel the molecular architecture linking dopamine, psychosis, and psychosocial stress. Included among the many genes associated with risk of schizophrenia are the gene encoding the dopamine D<sub>2</sub> receptor and those involved in the upstream regulation of dopaminergic synthesis, through glutamatergic and gamma-aminobutyric acidergic pathways. A number of these pathways are also linked to the stress response. We review these new lines of evidence and present a model of how genes and environmental factors may sensitize the dopamine system so that it is vulnerable to acute stress, leading to progressive dysregulation and the onset of psychosis. Finally, we consider the implications for rational drug development, in particular regionally selective dopaminergic modulation, and the potential of genetic factors to stratify patients.

**Keywords:** Dopamine, Etiology, Genetics, Neuroimaging, PET, Prodrome, Psychosis, Schizophrenia, Stress

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The dopamine hypothesis has been the leading pathoetiologic theory of schizophrenia for more than four decades (1–3). Our understanding of schizophrenia has progressed through advances in neuroimaging, epidemiology, and research into the prodromal phase that predates the onset of the disorder in many patients. Meanwhile, the role of genetic and environmental risk factors for schizophrenia has been clarified. Studies of how these risk factors affect the dopamine system, coupled with longitudinal studies during the prodrome, allow for a more refined understanding of what leads to the onset of psychosis. This review synthesizes the evidence on the nature of dopaminergic abnormalities in schizophrenia and its prodrome and how risk factors lead to illness, before considering the implications for treatment and prevention.

## ORIGINS OF THE DOPAMINE HYPOTHESIS

The origins of the dopamine hypothesis lie in two lines of evidence. First, clinical studies established that dopaminergic agonists and stimulants could induce psychosis in healthy individuals and could worsen psychosis in patients with schizophrenia (4,5). Second was the discovery that antipsychotic drugs affect the dopamine system (6). Later, the potency of antipsychotic drugs was linked to their affinity for

dopamine D<sub>2</sub> receptors, linking molecular action to clinical phenotype (7).

Postmortem studies provided the first direct evidence for dopaminergic dysfunction in the brain and its anatomical localization. These showed elevated levels of dopamine, its metabolites, and its receptors in the striata of people with schizophrenia (8,9). However, the studies were of patients who had received antipsychotic drugs. Consequently, it was not clear if the dysfunction was linked to onset or to an end-stage effect of the disorder or indeed was a consequence of antipsychotic drugs.

## IN VIVO IMAGING OF DOPAMINE IN SCHIZOPHRENIA

The development of positron emission tomography (PET) and single photon computed tomography specific radiotracers enabled the dopamine system to be studied in vivo with high molecular specificity (10).

Studies of the dopamine transporter (3,11) and vesicular monoamine transporter (12,13) availability in the striatum show no abnormality either in patients with a chronic condition or in drug-naïve first episode patients. Likewise, while meta-analysis has shown that there may be a small elevation in

**Table 1. PET Studies of the Dopaminergic System in Individuals at Increased Clinical Risk of Schizophrenia**

Study	Population	Radiotracer	Study Type	Region Reported	Findings (Standard Effect Size)	Additional Findings
Bloemen <i>et al.</i> , 2013 (29)	14 CHR 15 HV	[ <sup>123</sup> I]IBZM	Dopamine depletion	Striatum	—	Positive correlation between D <sub>2</sub> and D <sub>3</sub> receptor occupancy by dopamine and positive CHR symptoms
Howes <i>et al.</i> , 2009 (30)	24 CHR 12 HV	[ <sup>18</sup> F]-DOPA	Dopamine synthesis capacity	Striatum	↑ (0.75)	
Howes <i>et al.</i> , 2011 (32) <sup>a</sup>	30 CHR 29 HV	[ <sup>18</sup> F]-DOPA	Dopamine synthesis capacity	Striatum	↑ (1.18) <sup>a</sup>	No change in CHR subjects who did not convert to psychosis
Egerton <i>et al.</i> , 2013 (31)	26 CHR 20 HV	[ <sup>18</sup> F]-DOPA	Dopamine synthesis capacity	Striatum	↑ (0.81)	
Mizrahi <i>et al.</i> , 2012 (28)	12 CHR 12 HV	[ <sup>11</sup> C]-+ -PHNO	MIST-induced dopamine release	Striatum	↑ (0.98)	
Suridjan <i>et al.</i> , 2013 (27)	12 CHR 12 HV	[ <sup>11</sup> C]-+ -PHNO	D <sub>2</sub> <sup>high</sup> /D <sub>3</sub> receptor availability	Striatum, thalamus, globus pallidus, substantia nigra	—	
Abi-Dargham <i>et al.</i> , 2004 (132)	13 Scztyp 13 HV	[ <sup>123</sup> I]IBZM	Amphetamine-induced dopamine release	Striatum	↑ (0.93)	
Soliman <i>et al.</i> , 2008 (133) <sup>b</sup>	16 Scztyp 10 HV	[ <sup>11</sup> C]raclopride	MIST-induced dopamine release	Ventral striatum	↑	

CHR, clinical high risk of psychosis; HV, healthy volunteer; MIST, Montreal Imaging Stress Task; PET, positron emission tomography; Scztyp, schizotypal; ↑, significantly higher in patient group; ↓, significantly lower level in patient group; —, no significant difference; [<sup>123</sup>I]IBZM, [<sup>123</sup>I](S)-(-)-3-iodo-2-hydroxy-6-methoxy-N-[(1-ethyl-2-pyrrolidinyl)methyl]benzamide; [<sup>11</sup>C]-+ -PHNO, [11C]-(+)-4-propyl-9-hydroxynaphthoxazine; [<sup>18</sup>F]-DOPA, 6-[<sup>18</sup>F]fluoro-L-dihydroxyphenylalanine.

<sup>a</sup>Synthesis capacity increased only in subgroup that transitioned to psychosis (*n* = 9).

<sup>b</sup>MIST leads to significant decrease in tracer binding in subgroup characterized as potential schizotyp on the basis that subjects scored >1.95 SD on the negative subscale of Chapman schizotypy questionnaire.

dopamine D<sub>2/3</sub> receptor availability in schizophrenia, it is not reliably seen in patients naive for antipsychotic drugs (3).

Presynaptic dopaminergic function can be indexed either by using radiolabeled levo-dihydroxyphenylalanine or by measuring the change in radiotracer binding to D<sub>2/3</sub> receptors after a challenge designed to stimulate dopamine release. A significant elevation was reported in a meta-analysis of presynaptic dopaminergic function using these techniques (Cohen's *d* = 0.8) (3), and subsequent studies have reported even larger effect sizes (14–16). Furthermore, baseline occupancy of D<sub>2/3</sub> receptors by dopamine has also been found to be elevated, indicating higher synaptic dopamine levels at rest (17,18). Striatal dopamine release and baseline dopamine levels are closely correlated in schizophrenia (19), suggesting that the same abnormality underlies both.

While the striatum has received the greatest attention in PET studies, it has long been hypothesized that alterations in the dopamine system extend to additional brain regions (20). Dopaminergic hypofunction in the dorsolateral prefrontal cortex (DLPFC) has been proposed to account for negative and cognitive symptoms. Recently, people with schizophrenia have been found to show reduced dopamine release in the DLPFC after amphetamine challenge, and this release was shown to correlate with DLPFC activation during a working memory task (21). Meta-analysis of studies that have examined extrastriatal receptor densities indicate there are unlikely to be large differences in D<sub>2/3</sub> receptors and transporters in the regions studied, while the D<sub>1</sub> findings are inconsistent, potentially due to the effects of prior antipsychotic treatment (22).

## IN VIVO IMAGING OF DOPAMINE IN PEOPLE AT CLINICAL HIGH RISK OF PSYCHOSIS

The use of structured clinical assessments has made it possible to identify cohorts with prodromal symptoms, in which the risk of transition to psychosis can be as high as 40%, although recent studies have reported lower rates (23). Various studies have suggested that dopaminergic abnormalities exist in people at clinical high risk (CHR) of psychosis. Antipsychotic treatment trials have demonstrated efficacy of dopamine blockade in reducing prodromal-type symptom severity (24,25), and elevations in peripheral dopamine metabolites have been observed in CHR cohorts (26). However, these findings cannot tell us directly about central dopaminergic dysfunction; in this respect imaging has been particularly useful.

Three studies have examined D<sub>2/3</sub> receptor density in CHR populations; all showed no differences between groups (Table 1) (27–29). In two studies this could conceivably have been due to increased synaptic dopamine masking a difference in receptor densities (27,28). One study, however, addressed this with a dopamine depletion paradigm and showed no significant differences (29).

## Presynaptic Dopaminergic Function

Initial research showed that dopamine synthesis capacity was raised in CHR individuals (30) and was positively associated with the severity of prodromal-type symptoms (Table 1). This has subsequently been replicated (31) and found to be specific to prodromal individuals who progress to psychosis (32).

Furthermore, rescanning subjects as they developed psychosis showed that dopamine synthesis capacity increased further with the development of acute psychosis (33). In addition, greater dopamine release was found after psychological stress in CHR individuals compared with control subjects (15). The dopamine dysfunction was localized to the dorsal striatum, particularly areas functionally linked with the prefrontal cortex (PFC), and this was associated with altered function in frontal and temporal cortical regions (34,35). However, in contrast to findings in schizophrenia (17–19), dopamine depletion did not reveal differences in baseline synaptic levels of dopamine between at-risk individuals and healthy control subjects, although at-risk individuals reported symptomatic improvement after depletion (29). These findings indicate that while dopaminergic functioning is already dysregulated in those prodromal people who later progress to schizophrenia, it is not as marked as in patients with the disorder, and there is further dysregulation from the prodrome to psychosis.

## PSYCHOSOCIAL STRESS AND SCHIZOPHRENIA

In addition to genetic factors, neurodevelopmental hazards (36), and cannabis use (37), chronic psychosocial stressors, including childhood adversity (38), migration/ethnic minority status (39), and urbanicity (40), have become accepted as increasing the risk of schizophrenia. Furthermore, acute stress plays a role in triggering psychotic symptoms (41,42), and impaired stress tolerance is associated with prodromal symptoms (43).

## Effects of Psychosocial Stress on Dopamine

Animal studies consistently show that acute stressors (psychosocial and physical) lead to cortical dopamine release and that this dampens striatal dopamine release (44,45). Dopaminergic inhibition of cortical glutamatergic neurons projecting to

the striatum and midbrain is one pathway that potentially accounts for this (Figure 1) (46). The effects of chronic stress on the dopamine system vary by brain region and depend on the nature of the stress. In animals exposed to chronic stress, baseline levels of frontal dopaminergic activity are reduced, but responses to acute stress are elevated (47,48). With regard to the mesostriatal system, some studies suggest that chronic stress reduces dopaminergic responses to later activating stimuli (49–51), while others show increased release in response to subsequent amphetamine (52,53). It seems that prior exposure to chronic or inescapable stressors may down-regulate the system, while intermittent and escapable stress is more likely to have a sensitizing effect (51,54).

Studies of CHR individuals, individuals with schizophrenia, and first-degree relatives have shown that they produce a greater peripheral homovanillic acid response to stress (26,55,56). Two PET studies with healthy volunteers demonstrated more widespread cortical displacement of a  $D_{2/3}$  radiotracer during a stress task relative to a control task (57,58) (Table 2). In one of these studies a positive correlation between childhood adversity and extent of cortical dopamine release was observed (59). The researchers interpret this as potentially a resilience promoting mechanism. A study of first-degree relatives of individuals with schizophrenia showed less widespread cortical dopaminergic response to stress relative to healthy control subjects (60), and this was related to subjective stress and increased psychotic-like reactions to stress (61). Blunted cortical release of dopamine to amphetamine has been found in schizophrenia (21). However, a study of individuals with schizophrenia found no difference in the regional extent of cortical dopaminergic response to stress compared with control subjects, although the participants in this study had low symptom severity (62).

In the striatum, greater striatal dopamine release in response to acute social stress has been observed both in

**Table 2. PET Studies of the Effects of Acute and Chronic Stress on the Dopaminergic System**

Study	Population	Radiotracer	Findings
Nagano-Saito <i>et al.</i> , 2013 (58)	11 HV	[ $^{18}$ F]-fallypride MIST	Stress induces displacement in dmPFC, vmPFC, PCG (15.87%), thalamus, left caudate, right putamen; no displacement observed in amygdala or ventral striatum
Lataster <i>et al.</i> , 2011 (57)	12 HV	[ $^{18}$ F]-fallypride MIST	Stress induces displacement in PFC; vmPFC DA release associated with subjectively rated stress; extent of cortical release correlates with childhood adversity (59)
Heraus <i>et al.</i> , 2015 (62)	12 HV 12 NAPD	[ $^{18}$ F]-fallypride MIST	NAPD shows nonsignificantly $\downarrow$ stress-induced displacement in mPFC ( $d = 0.31$ )
Lataster <i>et al.</i> , 2014 (60)	11 HV 14 relatives	[ $^{18}$ F]-fallypride MIST	Relatives show $\downarrow$ proportion of voxels with displacement in mPFC (NS; $d = 0.46$ ); relatives showed association between increased stress and decreased displacement (control subjects showed opposite)
Mizrahi <i>et al.</i> , 2012 (28)	10 FEP 12 HV 12 CHR	PHNO MIST	DA release greatest for FEP, then CHR (in associated striatum); no increased release for HV; whole-striatum – CHR > HV ( $d = 0.98$ ); limbic striatum (0.65)
Pruessner <i>et al.</i> , 2004 (65)	5 Childhood high stress 5 Childhood low stress	Raclopride MIST	Childhood high-stress group show significantly $\uparrow$ ventral striatal displacement compared with the low-stress group
Oswald <i>et al.</i> , 2014 (66)	28 HV	Raclopride AMPH challenge	Past traumatic events and perceived stress associated with greater ventral striatal DA release
Egerton <i>et al.</i> , 2016 (64)	20 HV 47 CHR	[ $^{18}$ F]-DOPA	Physical and sexual abuse and unstable family arrangements associated with increased dopamine synthesis capacity

AMPH, amphetamine; CHR, clinical high risk; DA, dopamine; dmPFC, dorsomedial prefrontal cortex; FEP, first episode psychosis; HV, healthy volunteer; MIST, Montreal Imaging Stress Task; mPFC, medial prefrontal cortex; NAPD, nonaffective psychotic disorder; NS, nonsignificant; PCG, precentral gyrus; PET, positron emission tomography; PHNO, propyl-9-hydroxynaphthoxazine; vmPFC, ventromedial prefrontal cortex; [ $^{18}$ F]-DOPA, 6-[ $^{18}$ F]fluoro-L-dihydroxyphenylalanine.

individuals at risk of psychosis (15,63) and those with schizophrenia (28). In addition, greater dopamine synthesis capacity (64) and release [in response to stress (65) and amphetamine (66)] has been found in individuals exposed to childhood adversity. Greater dopamine release to amphetamine was also seen in people exposed to social isolation by virtue of hearing impairment (67).

### MOLECULAR MECHANISMS LINKING DOPAMINE, STRESS, AND PSYCHOSIS

A diathesis-stress model of schizophrenia proposes that the illness develops due to stress exposure acting on a pre-existing vulnerability (secondary to genetic factors or early environmental insults) (68,69). However, the molecular architecture underlying this relationship remains unclear. Genetic studies provide a means of identifying potential molecular mechanisms that underlie the disorder without the risk of confounding by treatment or other factors.

#### Genetics of Schizophrenia and the Dopamine System

Among the 108 loci associated with schizophrenia in the largest scale genomewide association study (GWAS) to date, one was for the D<sub>2</sub> receptor (70). Furthermore, a recent systematic pathway analysis of the Psychiatric Genomics Consortium's enlarged sample (PGC2) GWAS findings identified the top pathway for genes associated with schizophrenia as being that for dopaminergic synapse (71) (Holmans P, Ph.D., personal communication, October 2015). However, this is a large set of genes, which includes many involved more widely in neurotransmission and signaling, that impinge indirectly on dopaminergic transmission. For example, both alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid and *N*-methyl-D-aspartate (NMDA) receptor subtypes are included. A more recent analysis of the PGC2 GWAS data focused on a set of 11 genes more directly related to dopamine synthesis, metabolism, and neurotransmission (72). This confirmed the association with single nucleotide polymorphisms (SNPs) in the vicinity of *DRD2*, but the analysis found no evidence for enrichment in the other genes or in the set as a whole. While these results do not add further support to the hypothesis that direct effects on dopaminergic neurotransmission partially mediate genetic susceptibility to schizophrenia, they do not exclude a role for rare variants in core dopaminergic genes or other mutational mechanisms such as repeat sequences that are poorly tagged in GWAS studies. It remains to be determined whether there is enrichment of genetic signal in other restricted gene sets relating to dopaminergic function, such as signal transduction and postsynaptic signaling. It is also possible that dopaminergic genes play a more prominent role in clinical subsets of schizophrenia or in cases defined on the basis of drug response.

The finding from PGC2 that SNPs at the *DRD2* locus are associated with schizophrenia is of great potential relevance to understanding the role of dopaminergic neurotransmission in the disorder and to identifying upstream and downstream mechanisms. However, it is possible that the associated SNP(s) are modulating the function of another gene either in *cis* or *trans* rather than *DRD2* itself. There is thus a pressing

need to determine how, where, and at what developmental stage(s) this association affects mechanistically on gene function. As well as confirming an etiologic role for dopamine dysfunction this might be expected to provide important new insights into the nature of dopamine system dysfunction in the disorder.

Genes involved in dopaminergic neurotransmission downstream of the synapse have also been linked to an increased risk of schizophrenia. Postsynaptic dopamine neurotransmission includes kinases such as the serine-threonine kinase Akt. Akt3 was associated with schizophrenia in the GWAS described above (70), while Akt1 has been linked to schizophrenia in other studies (73,74). Functional changes to postsynaptic signal transduction could conceivably alter regulatory feedback onto presynaptic dopaminergic neurons (75).

#### Genetics of Psychosocial Stress and the Dopamine System

Gene-environment studies using epidemiologic approaches have demonstrated interactions between genetic and psychosocial risk factors for schizophrenia (76–78). The importance of environmental effects may explain why the dopamine imaging evidence is inconsistent in people who may carry genetic risk of schizophrenia, such as relatives of people with schizophrenia, both in terms of dopamine synthesis capacity (79,80) and D<sub>1</sub> (81) and D<sub>2</sub> (82,83) receptor availability (Table 3). Below we discuss genes that may mediate the relationship between stress exposure, dopaminergic functioning, and psychosis (Table 4).

Catechol-O-methyltransferase (COMT), a major dopamine catabolic enzyme, was implicated in early candidate gene studies and is located within one of the strongest genetic risk factors for schizophrenia, a 1.5- to 3-Mb deletion at 22q.11.2 (84). COMT contains a functional polymorphism involving a valine (Val) to methionine (Met) substitution. The functional consequences of variation at this locus have been widely studied, but it should be noted that there was no evidence for association of the Val/Met variant with schizophrenia in the PGC2 (85). The Met allele is associated with reduced catabolic activity and is linked to greater tonic and reduced phasic striatal dopaminergic transmission (86). In the cortex, a PET study investigating D<sub>1</sub> receptor density suggested that the Val allele was associated with lower levels of baseline dopamine (87), although no association was observed in a study of cortical D<sub>2</sub> receptors (88). A study examining stress-induced cortical dopamine release suggested the Met allele was associated with reduced release (and a greater subjective stress response) (89).

Stress-induced catecholamine release can impair working memory (90). During acute stress, Met homozygotes show impairments in working memory performance and reduced PFC activation, while Val carriers show the opposite effects (91,92). This has been interpreted in terms of the inverted-U relationship between dopamine levels and cognitive function. The greater level of dopaminergic function at baseline in Met carriers means an increase impairs performance, whereas in the case of the Val allele, the increase is beneficial.

In terms of chronic stress, Met homozygosity has been associated with a negative relationship between the number of stressful life events and hippocampal volume, while the opposite relationship is seen for Val homozygosity (93).



**Table 3. PET Studies of the Dopaminergic System in Individuals at Increased Genetic Risk of Schizophrenia**

Study	Population	Phenotype	Radiotracer	Study Type	Region Reported	Change in Genetic High-Risk Group (Standard Effect Size)
Brunelin et al., 2010 (134)	8 GHR 10 HV	Siblings of patients with schizophrenia	[ <sup>11</sup> C]raclopride	2DG induced dopamine release	Whole striatum GHR subjects show greater asymmetry between left and right striatum; no differences in DA release in ventral striatum	↑
Huttunen et al., 2008 (80)	17 GHR 17 HV	First-degree relatives of patients with schizophrenia	[ <sup>18</sup> F]-DOPA	Dopamine synthesis capacity	Caudate and putamen No differences observed in ventral striatum	↑
Shotbolt et al., 2011 (79)	6 GHR 20 HV	Co-twins of patients with schizophrenia	[ <sup>18</sup> F]-DOPA	Dopamine synthesis capacity	Whole striatum	–
Hirvonen et al., 2005 (83)	6 MZ 5 DZ 14 HV	Co-twins of patients with schizophrenia	[ <sup>11</sup> C]raclopride	D <sub>2/3</sub> receptor density	Caudate No differences observed in putamen or thalamus	↑ (0.85)
Hirvonen et al., 2006 (81)	6 MZ 5 DZ 13 HV	Co-twins of patients with schizophrenia	[ <sup>11</sup> C]SCH 23390	D <sub>1</sub> receptor density	mPFC, STG, and angular gyrus	↑
Hirvonen et al., 2006 (135)	6 MZ 5 DZ 13 HV	Co-twins of patients with schizophrenia	[ <sup>11</sup> C]SCH 23390, [ <sup>11</sup> C]raclopride	D <sub>1</sub> :D <sub>2/3</sub> ratio	Caudate and putamen	–
Lee et al., 2008 (83)	11 GHR 11 HV	First- and second-degree relatives of patients with schizophrenia	[ <sup>11</sup> C]raclopride	Striatal D <sub>2/3</sub> receptor density	Caudate and putamen GHR subjects show ↓ asymmetry of receptor density in putamen	–

DA, dopamine; DZ, dizygotic; GHR, genetic high risk; HV, healthy volunteer; mPFC, medial prefrontal cortex; MZ, monozygotic; PET, positron emission tomography; STG, superior temporal gyrus; –, no significant difference; 2DG, 2-deoxy-D-glucose; [<sup>18</sup>F]-DOPA, 6-[<sup>18</sup>F]fluoro-L-dihydroxyphenylalanine.

In Val homozygotes increased lifetime stress was found to correlate with reduced methylation that in turn correlated with poorer working memory performance (94). The Val allele has a methylation site absent on the Met allele; it may be that increased methylation in Val homozygotes leads to reduced gene expression, leading to individuals' COMT having activity similar to a Met carrier.

Similarly to COMT, brain-derived neurotrophic factor has a Val/Met functional polymorphism. A PET study of brain-derived neurotrophic factor polymorphisms showed that Met carriers had greater striatal dopamine release in the context of a pain stressor (95). Consistent with this finding, the Met allele has been associated with increased stress-induced paranoia in healthy individuals (96).

The expression and functioning of *DRD2* is affected by both genetic polymorphisms and environmental factors. In a healthy volunteer study, heterozygotes for a *DRD2* SNP showed greater stress-induced striatal dopamine release than homozygotes (97). An animal study showed increased D<sub>2</sub> receptor density in the nucleus accumbens after early life maternal deprivation, but only in heterozygotes for a separate *DRD2* polymorphism (98).

In contrast to studies of synaptic and postsynaptic dopamine genes, there have been fewer for presynaptic genes, such as those for synthetic enzymes and proteins regulating presynaptic storage of dopamine. While the few published studies are inconsistent (99–101), this is an area that warrants investigation, given the imaging findings. Disrupted in schizophrenia 1 (*DISC1*) is involved in a pathway that regulates presynaptic dopaminergic function, is one of the best-studied loci linked to an increased risk of schizophrenia (102), and displays abnormal expression in induced pluripotent stem cells from individuals with schizophrenia (103).

Animal models have demonstrated that alterations in *DISC1* can lead both to impaired development of mesocortical dopaminergic neurons and to increased amphetamine-induced striatal dopamine release (104). Adolescent isolation stress has been shown to lead to behavioral abnormalities only in mice with *DISC1* mutations, secondary to glucocorticoid-mediated changes to the functioning of mesocortical dopaminergic pathways (105). *DISC1* is also involved in anchoring phosphodiesterase 4A (*PDE4A*) next to the spine apparatus (106). The gene coding for *PDE4A* has also been linked to schizophrenia (107), and both *DISC* and *PDE4A* together modulate stress signaling pathways. Impairment of *DISC1* reduces its ability to anchor *PDE4A*, and this in turn leads to a disinhibition of the stress response and accompanying PFC impairment (108).

## RELATIONSHIP BETWEEN DOPAMINE AND OTHER NEUROTRANSMITTERS

*DISC1* is also involved in glutamatergic neurotransmission (102). Furthermore, both GWAS and copy number variant studies have implicated other genes involved in glutamatergic neurotransmission, including NMDA and other glutamatergic receptors (109). There is evidence that NMDA hypofunction disrupts the inhibitory/excitatory equilibrium at interneurons and thereby leads to increased dopamine release (110–112) (Figure 1; [see (113)]). Neurons derived from induced

**Table 4. Genes Related to Dopaminergic Functioning, Schizophrenia, and Stress**

Gene	Function	Relationship to Dopamine, Stress, and Schizophrenia
<i>AKT1</i> <i>AKT3</i>	Serine threonine kinases involved in postsynaptic dopaminergic neurotransmission	Changes in postsynaptic signal transduction could lead to hypersensitivity to dopamine and alter presynaptic feedback. <i>AKT1</i> has been linked to Scz in two studies (73,74), whereas <i>AKT3</i> has been implicated in GWAS.
<i>BDNF</i>	A neurotrophin that encourages the survival, growth, and differentiation of neurons	Met carriers show greater striatal DA release in the context of a pain stressor, and has been associated with greater stress-induced paranoia.
<i>COMT</i>	Catabolizes dopamine (particularly cortical); Met allele associated with reduced catabolic activity	Met allele has been linked to reduced stress-induced cortical DA release. Chronic stress has been associated with greater reductions in hippocampal volume in Met homozygotes.
<i>DISC1</i>	Participates in a wide range of cell functions; involved in regulation presynaptic dopaminergic function and also in anchoring PDE4A to spine apparatus	Animal models demonstrate <i>DISC1</i> alterations can impair development of mesocortical DA neurons and lead to increased AMPH-induced striatal DA release. Adolescent stress has been shown to lead to behavior abnormalities only in mice with <i>DISC1</i> mutations. Linked to Scz in multiple studies.
<i>DRD2</i>	Dopamine receptor 2	Changes in presynaptic and postsynaptic receptor density or function may have marked effects on dopaminergic signaling. SNP has been associated with greater stress induced DA release. Animal study demonstrated a certain SNP is associated with increased D <sub>2</sub> R density in the nucleus accumbens after maternal deprivation. Locus associated in schizophrenia GWAS.
<i>PDE4A</i>	Involved in a variety of responses to extracellular signals	Together with <i>DISC1</i> involved in modulation of stress signaling pathways, impairment leads to disinhibition of the stress response and PFC impairment. Has been linked to schizophrenia.

AMPH, amphetamine; DA, dopamine; D<sub>2</sub>R, D<sub>2</sub> dopamine receptor; GWAS, genomewide association study; Met, methionine; PFC, prefrontal cortex; Scz, schizophrenia; SNP, single nucleotide polymorphism.

pluripotent stem cells from patients with schizophrenia show greater basal and activity-dependent dopamine secretion (114), as well as reduced glutamate receptor and altered DISC1 expression (103). Glutamatergic neurotransmission also mediates the effects of both acute and chronic stress (115).

Recent evidence from more than 11,000 patients with schizophrenia and 16,000 control subjects has also shown an enrichment of copy number variants involving glutamatergic and gamma-aminobutyric acidergic (GABAergic) systems (116). These systems have excitatory and inhibitory effects, respectively, on dopaminergic function, suggesting that the genetic variants in these systems may alter the regulation of dopamine in schizophrenia. Thus, it is plausible that a number of the genetic risk variants in upstream pathways modulate dopamine function. Future studies must first clarify the molecular pathways and links between the genetic variants and effects on glutamatergic and GABAergic neuronal function before the link to downstream dopaminergic effects can be tested.

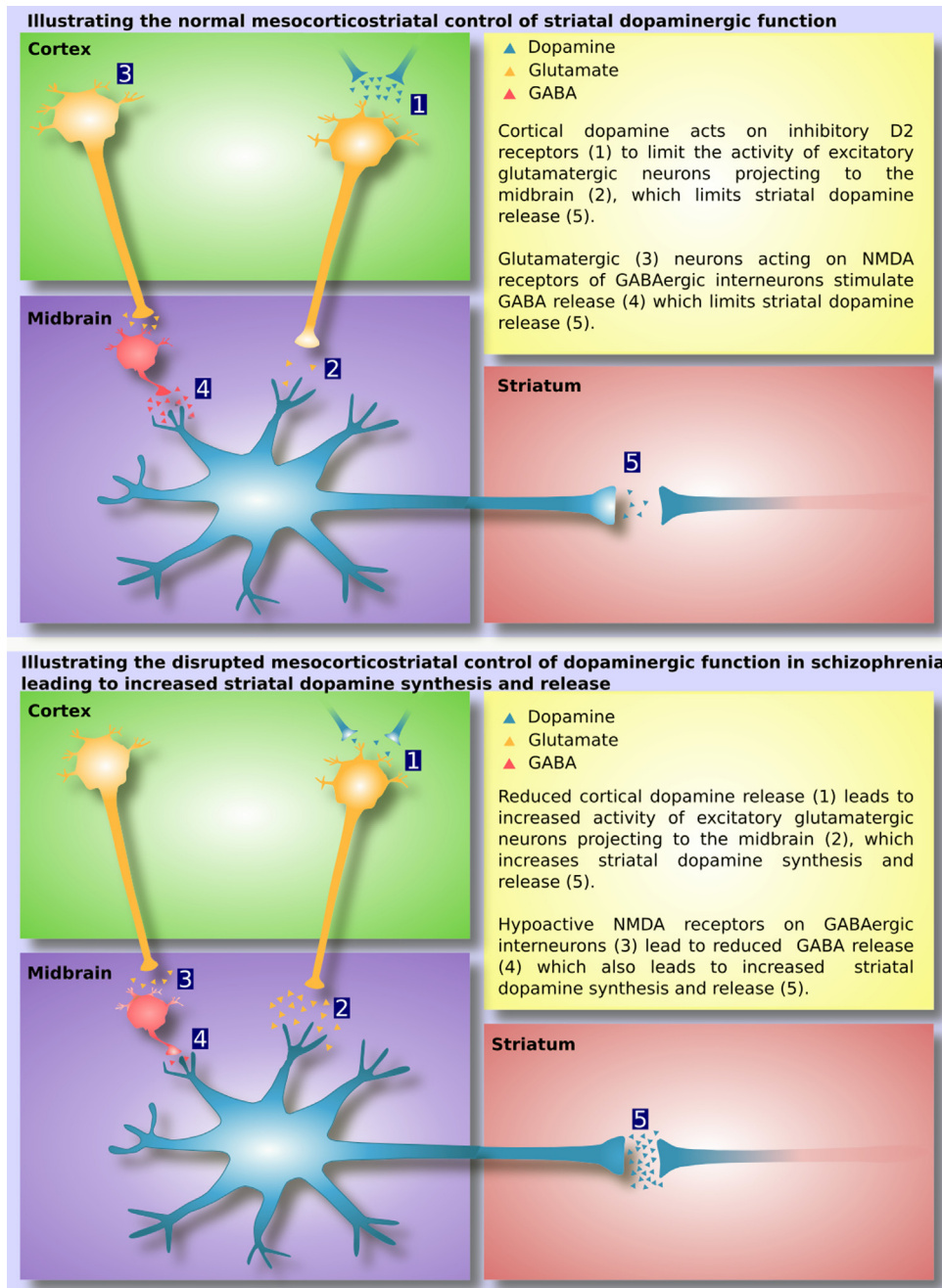
### INTEGRATING THE IMAGING, STRESS, AND GENETIC FINDINGS

Collectively, the imaging findings identify increased striatal presynaptic synthesis and release of dopamine as the major locus of dopaminergic dysfunction in schizophrenia. Furthermore, it appears this dysfunction is also present in the prodrome and is linked to the clinical development of the disorder. This suggests that presynaptic striatal dopamine dysfunction plays a causal role in the development of psychosis.

The genetic findings have not implicated genes directly involved in determining dopamine synthesis or release but instead point to upstream and downstream pathways linked to

the dopamine system. A number of the genetic risk factors converge on upstream pathways, particularly those involving glutamatergic systems. Because glutamatergic projections to the striatum and midbrain regulate presynaptic dopaminergic function, genetic variants affecting glutamatergic function could alter the regulation of dopaminergic function. The net effect of this may be to reduce the homeostatic control of midbrain dopamine neurons, making them more vulnerable to sensitization by the sociodevelopmental risk factors described above. In addition, a number of other genetic risk factors affect dopamine receptors and postsynaptic signal transduction pathways to modulate postsynaptic dopaminergic neurotransmission. The net effect of this may be to increase the sensitivity of the medium spiny neurons in the striatum to dopamine. This suggests that the genetic risk factors for schizophrenia may play two roles: the upstream factors render the dopamine neurons vulnerable to dysregulation, while the downstream factors amplify the effects of dysregulation.

We have also discussed the effect of stress on the corticostriatal dopamine system and how genetic and environmental influences moderate this. Recent studies in patients with schizophrenia and their relatives show blunted cortical dopamine release to be a challenge. This is likely to reduce the inhibition of mesostriatal dopamine release and result in augmented stress-induced striatal release of dopamine. The preclinical findings suggest that this involves glutamatergic projections to the striatum and midbrain acting on GABAergic interneurons, both of which may be hypofunctional due to genetic risk variants affecting glutamatergic and GABAergic receptors linked to schizophrenia. Thus, blunted cortical dopaminergic release to stress coupled with impaired glutamatergic regulation of dopamine neurons may act on a sensitized mesostriatal dopamine system to result in increased striatal dopamine dysfunction (Figure 2).



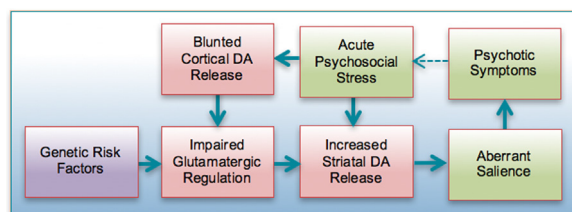
**Figure 1.** The regulation of mesostriatal dopaminergic function by cortical glutamatergic projections and gamma-aminobutyric acidergic (GABAergic) interneurons. DA, dopamine; NMDA, *N*-methyl-D-aspartate.

## TREATMENT IMPLICATIONS

Current pharmacologic treatments for schizophrenia primarily operate as postsynaptic  $D_{2/3}$  receptor antagonists (117). While these bring symptomatic relief, they do not target the underlying pathophysiology; even patients who have responded to antipsychotic drugs show elevated striatal dopamine synthesis capacity (118). Furthermore, antipsychotic drugs show limited effectiveness in targeting negative and cognitive symptoms.

Given the evidence that cognitive symptoms are linked to cortical hypofunction, including reduced cortical dopamine

release, it is unsurprising that dopamine blockade does not help these symptoms. Furthermore, antidopaminergic blockade of ventral striatal regions may impair motivation and affective processing and so worsen negative symptoms. A clear implication is that we need regionally selective treatments, dampening dopamine neurotransmission in the striatum, specifically the dorsal striatum where dopamine elevation is most marked, and augmenting it in the cortex. Animal studies suggest that some existing pharmacologic agents such as mirtazapine may be able to selectively augment cortical dopamine transmission. Interestingly, mirtazapine is



**Figure 2.** Model integrating genetic and environmental factors, dopaminergic dysregulation, and the development of psychotic symptoms. DA, dopamine.

used as a treatment in stress-related disorders (119), and it may be an effective adjunctive treatment for negative symptoms in schizophrenia (120).

Upstream and downstream genetic factors may have implications for treatment. Putatively, people with a high loading for upstream genetic risk might show marked presynaptic dopamine dysfunction, while those with a high loading for postsynaptic risk might show minimal presynaptic dysfunction but would be highly sensitive to the effects of even small amounts of dopamine release. There is evidence that a subgroup of individuals with schizophrenia and comorbid substance dependence (121) or cannabis-induced psychotic symptoms (122) do not show increased dopamine synthesis or release and that sensitivity to the psychotogenic effects of cannabis is linked to these downstream genetic risk factors. Individuals predominantly affected by downstream factors might be more sensitive to the side effects of  $D_{2/3}$  receptor blockade (123), but they might tolerate partial agonists better.

## LIMITATIONS

A number of the aspects of the model described await testing. It remains to be established if genetic and environmental factors interact to sensitize the dopamine system, if there is blunted cortical dopamine release in the prodrome, and if blunted cortical dopaminergic function leads to striatal hyperdopaminergia. Moreover, while preclinical evidence supports the glutamatergic circuit regulating dopamine, the specifics remain to be tested in humans, and reverse causality is yet to be excluded.

A number of the COMT findings are difficult to integrate into the model. There is no evidence from GWASs to support association with SNPs in COMT. In healthy individuals, the Val allele is associated with increased social stress-induced paranoia (96,124). This allele has also been associated with greater symptom severity in individuals with psychotic disorders (125,126). However, in individuals with a psychotic disorder, Met homozygotes demonstrate increased psychotic reactivity to stress (127,128). This does not fit with a model in which reduced Met activity would be protective for individuals with a psychotic disorder, where we propose a deficit of cortical dopamine. This inconsistency may be due to the precise nature of the stressors under examination or potentially due to gene-gene-environment interactions.

While glutamatergic and GABAergic alterations have been reported in neuroimaging studies of schizophrenia (110,129) and the prodrome (130), the precise molecular abnormalities remain to be determined in vivo. The links between

glutamatergic dysregulation and dopaminergic signaling remain to be determined in schizophrenia (110), although there is some evidence of this in the prodrome (131).

## CONCLUSIONS

Altered presynaptic striatal dopamine synthesis and release are consistently seen in schizophrenia. This is also seen to a lesser degree in the prodrome and becomes worse as frank psychosis manifests. Blunted cortical dopamine release has now been demonstrated in schizophrenia, and there is increasing evidence that altered cortical function is linked to striatal dopamine hyperactivity in people with prodromal symptoms, indicating a central role for corticostriatal dysregulation. Furthermore, it is now possible to begin to understand how genetic and environmental risk factors may lead to striatal dopamine dysregulation by impairing the cortical regulation of midbrain dopamine neurons. However, the precise molecular mechanisms remain to be fully elucidated, and blunted cortical dopamine release has yet to be investigated in the prodrome. Nevertheless, half a century on from the initial formulations of the dopamine hypothesis, it is possible to see what we need to do to rationally design medications that target the pathophysiology underlying the onset of the disorder to treat it or indeed potentially to prevent it.

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