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# The role of genes, stress and dopamine in the development of schizophrenia

**Dr Oliver D Howes, MRCPsych PhD DM**[1,2], **Dr Robert McCutcheon, MRCPsych**[1,2], **Prof Michael J Owen, PhD FRCPsych**[3], and **Prof Robin Murray, FRS DSc**[1]

[1]Psychosis Studies, King's College London, Camberwell, London, SE5 8AF, UK, TEL: + 44 207 848 0080; FAX: + 44 207 848 0976

[2]MRC Clinical Sciences Centre, Imperial College Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

[3]MRC Centre for Neuropsychiatric Genetics and Genomics, and Neuroscience and Mental Health Research Institute, Cardiff University

## Abstract

The dopamine hypothesis is the longest standing pathoaetiological theory of schizophrenia. As 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 impact on 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 DRD2 receptor and those involved in the up-stream regulation of dopaminergic synthesis, through glutamatergic and gamma-aminobutyric acid (GABA)-ergic 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 sensitise 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.

Corresponding Author: Oliver D Howes Psychosis Studies, King's College London, Camberwell, London, SE5 8AF, UK, TEL: + 44 207 848 0080; FAX: + 44 207 848 0976; oliver.howes@kcl.ac.uk.

**Conflicts of interest**

Dr Howes and Prof Murray have received investigator-initiated research funding from and/or participated in advisory/ speaker meetings organised by pharmaceutical companies including Astra-Zeneca, Autifony, BMS, Eli Lilly, Jansenn, Lundbeck, Lyden-Delta, Otsuka, Servier, Sunovion, and Roche. Neither they nor their immediate families have been employed by or have holdings/ a financial stake in any biomedical company. Dr McCutcheon and Prof Owen have no potential conflicts of interest.


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## Introduction

The dopamine hypothesis has been the leading pathoaetiological theory of schizophrenia for over 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 impact on 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.

## The 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 worsen psychosis in patients with schizophrenia (4; 5). Second, was the discovery that antipsychotic drugs affect the dopamine system (6). Later, the potency of antipsychotics was linked to their affinity for dopamine D2 receptors - linking molecular action to clinical phenotype (7).

Post-mortem 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 antipsychotics. Consequently, it was not clear if the dysfunction was linked to onset, or an end-stage effect of the disorder, or indeed a consequence of antipsychotics.

## In vivo imaging of dopamine in schizophrenia

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

Studies of the dopamine transporter (DAT) (3; 11) and vesicular monoamine transporter (VMAT) (12; 13) availability in the striatum show no abnormality either in chronic patients or in drug naïve first episode patients. Likewise, while meta-analysis has shown that there may be a small elevation in dopamine D2/3 receptor availability in schizophrenia, it is not reliably seen in antipsychotic-naive patients (3).





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Presynaptic dopaminergic function can be indexed using either radiolabelled l-dihydroxyphenylalanine (*l*-dopa), or one can measure the change in radiotracer binding to D2/3 receptors following 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 D2/3 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 following 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 extra-striatal receptor densities indicate there are unlikely to be large differences in D2/3 receptors and transporters in the regions studied, whilst the D1 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%, though 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 D2/3 receptor density in CHR populations; all showing no differences between groups (see 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 positively associated with the severity of prodromal-type symptoms (see table 1). This has subsequently been replicated (31), and found to be specific to prodromal individuals who progress to psychosis (32). Furthermore, re-scanning subjects as they developed psychosis showed that dopamine synthesis capacity increases further with the development of acute psychosis (33). Additionally, greater dopamine release was found

following psychological stress in CHR individuals compared to controls (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 controls, although at risk individuals reported symptomatic improvement following depletion (29). These findings indicate that whilst 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).

### The 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 (53; 54). Dopaminergic inhibition of cortical glutamatergic neurons projecting to the striatum and midbrain is one pathway that potentially accounts for this (see figure 1) (55). 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 (56; 57). With regard to the mesostriatal system, some studies suggest that chronic stress reduces dopaminergic responses to later activating stimuli (58–60), while others show increased release in response to subsequent amphetamine (61; 62). 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 sensitising effect (60; 63).

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; 64; 65). Two healthy volunteer PET studies demonstrated more widespread cortical displacement of a D2/3 radiotracer during a stress task relative to a control task (66; 67) (see table 3). In one of these a positive correlation between childhood adversity and extent of cortical dopamine release was observed (68). The authors 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 controls (69), and this was related to subjective stress and increased psychotic-like reactions to stress (70). 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 to controls, although the participants in this study had low symptom severity (71).

In the striatum, greater striatal dopamine release in response to acute social stress has been observed both in individuals at risk for psychosis (15; 76) and those with schizophrenia (28). Additionally, greater dopamine synthesis capacity (72), and release (in response to stress (73) and amphetamine (74)) 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 (75).

## 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) (77; 78). 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.

### The genetics of schizophrenia and the dopamine system

Amongst the 108 loci associated with schizophrenia in the largest scale GWAS to date, one was for the dopamine receptor 2 (D2) (79). Furthermore a recent systematic pathway analysis of the Psychiatric Genetics Consortium's enlarged sample (PGC2) GWAS findings identified the top pathway for genes associated with schizophrenia as being that for dopaminergic synapse (80) (Holmans P, personal communication). However, this is a large set of genes, which includes many involved more widely in neurotransmission and signalling, that impinge indirectly on dopaminergic transmission. For example both AMPA and NMDA receptor subtypes are included. A more recent analysis of the PGC2 GWAS data focussed on a set of 11 genes more directly related to dopamine synthesis, metabolism and neurotransmission (81). This confirmed the association with SNPs in the vicinity of *DRD2*, but 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 post-synaptic signalling. 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 impacts mechanistically on gene function. As well as

confirming an aetiological 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. Post-synaptic dopamine neurotransmission includes kinases such as the serine-threonine kinase Akt. Akt3 was associated with schizophrenia in the GWAS described above (79), while Akt1 has been linked to schizophrenia in other studies (82; 83). Functional changes to post-synaptic signal transduction could conceivably alter regulatory feedback onto presynaptic dopaminergic neurons (84).

## The genetics of psychosocial stress and the dopamine system

Gene-environment studies using epidemiological approaches have demonstrated interactions between genetic and psychosocial risk factors for schizophrenia (85–87). The importance of environmental effects may explain why the dopamine imaging evidence is inconsistent in people who may carry genetic risk for schizophrenia, such as relatives of people with schizophrenia, both in terms of dopamine synthesis capacity (88; 89), and D1 (90) and D2 (91; 92) receptor availability (see table 2). Below we discuss genes that may mediate the relationship between stress exposure, dopaminergic functioning, and psychosis.

Catechol-O-methyltransferase (COMT, a major dopamine catabolic enzymes) was implicated in early candidate gene studies, and is located within one of the strongest genetic risk factors for schizophrenia, a 1.5-3 Mb deletion at 22q.11.2. (93) 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 born in mind that there was no evidence for association of the Val/Met variant with schizophrenia in the PGC2 (95). The Met allele is associated with reduced catabolic activity, and is linked to greater tonic and reduced phasic striatal dopaminergic transmission (96). In the cortex, a PET study investigating D1 receptor density suggested that the Val allele was associated with lower levels of baseline dopamine(99) (although no association was observed in a study of cortical D2 receptors) (98). A study examining stress induced cortical dopamine release suggested the Met allele was associated with reduced release (and a greater subjective stress response) (99).

Stress induced catecholamine release can impair working memory (100). During acute stress, Met homozygotes show impairments in working memory performance and reduced PFC activation, while Val carriers show the opposite effects (101; 102). 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 homozgosity (103). In Val homozygotes increased lifetime stress was found to correlate with reduced methylation which in turn correlated with

poorer working memory performance (104). 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 (BDNF) has a Val/Met functional polymorphism. A PET study of BDNF polymorphisms showed that Met carriers had greater striatal dopamine release in the context of a pain stressor (105). Consistent with this finding, the Met allele has been associated with increased stress induced paranoia in healthy individuals (106).

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 compared to homozygotes (107). An animal study showed increased D2 receptor density in the nucleus accumbens following early life maternal deprivation, but only in heterozygotes for a separate DRD2 polymorphism (108).

In contrast to studies of synaptic and post-synaptic dopamine genes, there have been fewer for presynaptic genes, such as those for synthetic enzymes and proteins regulating presynaptic storage of dopamine. Whilst the few published studies are inconsistent (109–111), this is an area that warrants investigation given the imaging findings. Disrupted In Schizophrenia (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 (112), and displays abnormal expression in induced pluripotent stem cells (IPSCs) from individuals with schizophrenia (113). Animal models have demonstrated that alterations in DISC1 can lead to both impaired development of mesocortical dopaminergic neurons, and increased amphetamine induced striatal dopamine release (114). Adolescent isolation stress has been shown to lead to behavioural abnormalities only in mice with DISC1 mutations, secondary to glucocorticoid mediated changes to the functioning of mesocortical dopaminergic pathways (115). DISC1 is also involved in anchoring phosphodiesterase 4A (PDE4A) next to the spine apparatus (116). The gene coding for PDE4A has also been linked to schizophrenia (117), and both DISC and PDE4A together modulate modulate stress signalling 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 (122).

## The relationship between dopamine and other neurotransmitters

DISC1 is also involved in glutamatergic neurotransmission (112). Furthermore, both GWAS and copy number variant (CNV) studies have implicated other genes involved in glutamatergic neurotransmission, including N-Methyl-D-Aspartate (NMDA) and other glutamatergic receptors (123). There is evidence that NMDA hypofunction disrupts the inhibitory/excitatory equilibrium at interneurons and thereby leads to increased dopamine release (see figure 1 and Abi-Dargham et al also in this issue) (124–126). Neurons derived from IPSCs from patients with schizophrenia show greater basal and activity dependent dopamine secretion (127), as well as reduced glutamate receptor and altered DISC1 expression (113). Glutamatergic neurotransmission is also mediates the effects of both acute and chronic stress (128).

Recent evidence from over 11,000 patients with schizophrenia and 16,000 controls has also shown an enrichment of CNVs involving glutamatergic and GABAergic systems (129). 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 down-stream 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 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 up-stream and down-stream pathways linked to the dopamine system. A number of the genetic risk factors converge on up-stream pathways, particularly those involving glutamatergic systems. As 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 sensitisation by the socio-developmental risk factors described above. In addition, a number of other genetic risk factors impact on dopamine receptors and post-synaptic signal transduction pathways, to modulate post-synaptic 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 up-stream factors render the dopamine neurons vulnerable to dysregulation, whilst the down-stream factors amplify the effects of dysregulation.

We have also discussed the effect of stress on the cortico-striatal 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 a challenge. This is likely to reduce the inhibition of meso-striatal 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 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 (see figure 2).

## Treatment Implications

Current pharmacological treatments for schizophrenia primarily operate as post-synaptic D2/3 receptor antagonists (130). Whilst these bring symptomatic relief, they do not target the underlying pathophysiology - even patients who have responded to antipsychotics show elevated striatal dopamine synthesis capacity (131). Furthermore, antipsychotics 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, anti-dopaminergic 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 pharmacological agents such as mirtazapine may be able to selectively augment cortical dopamine transmission. Interestingly, mirtazapine is used as a treatment in stress related disorders (133), and it may be an effective adjunctive treatment for negative symptoms in schizophrenia (134).

Up-stream and down-stream genetic factors may have implications for treatment. Putatively people with a high loading for up-stream genetic risk might show marked presynaptic dopamine dysfunction, whilst those with a high loading for post-synaptic 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 co-morbid substance dependence (135) or cannabis-induced psychotic symptoms (49) do not show increased dopamine synthesis or release, and that sensitivity to the psychotogenic effects of cannabis is linked to these down-stream genetic risk factors. Individuals predominantly affected by down-stream factors might be more sensitive to the side-effects of D2/3 receptor blockade (136), but 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, whilst 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 GWAS supporting association with SNPs in COMT. In healthy individuals, the Val allele is associated with increased social stress induced paranoia (106; 137). This allele has also been associated with greater symptom severity in individuals with psychotic disorders (138; 139). However, in individuals with a psychotic disorder, Met homozygotes demonstrate increased psychotic reactivity to stress (140; 141). This does not fit with a

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model where 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.

Whilst glutamatergic and GABAergic alterations have been reported in neuroimaging studies of schizophrenia (124; 142), and the prodrome (143), the precise molecular abnormalities remain to be determined in vivo. The links between glutamatergic dysregulation and dopaminergic signalling remain to be determined in schizophrenia (124), although there is some evidence of this in the prodrome (144).

## Conclusions

Altered presynaptic striatal dopamine synthesis and release is 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 cortico-striatal 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 in order to rationally design medications that target the pathophysiology underlying the onset of the disorder to treat it, or indeed potentially prevent it.

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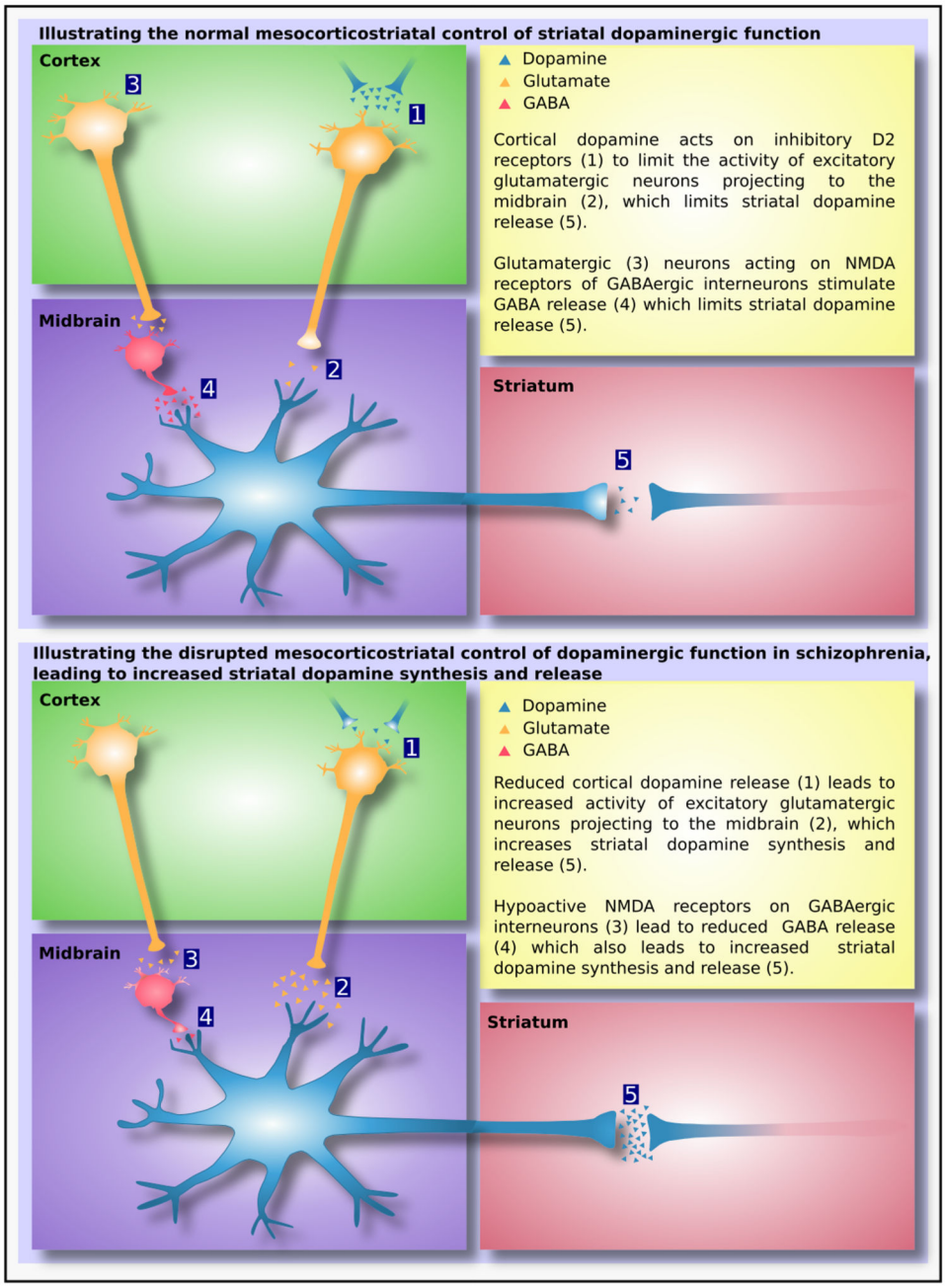


**Figure 1.**

The regulation of mesostriatal dopaminergic function by cortical glutamatergic projections and GABAergic interneurons

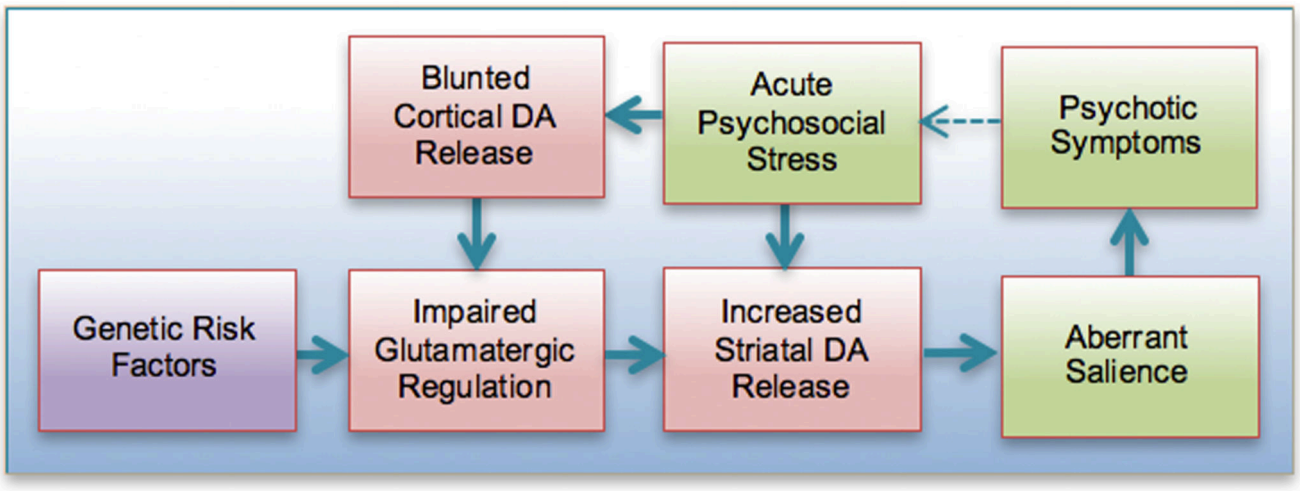


**Figure 2.**

Model integrating genetic and environmental factors, dopaminergic dysregulation and the development of psychotic symptoms (DA=dopamine)



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**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 *et al.* 2013(29) | 14 CHR<br>15 HV | [$^{123}$I]IBZM | Dopamine depletion | Striatum | - | Positive correlation between D2/3 receptor occupancy by dopamine and positive CHR symptoms |
| Howes *et al.* 2009 (30) | 24 CHR<br>12 HV | [$^{18}$F]-DOPA | Dopamine synthesis capacity | Striatum | ↑ (0.75) | |
| Howes *et al.* 2011b(32) [a] | 30 CHR<br>29 HV | [$^{18}$F]-DOPA | Dopamine synthesis capacity | Striatum | ↑(1.18)[a] | No change in CHR subjects who did not convert to psychosis |
| Mizrahi *et al.* 2012(28) | 12 CHR<br>12 HV | [$^{11}$C]-+-PHNO | MIST induced dopamine release | Striatum | ↑(0.98) | |
| Suridjan *et al.* 2013 (27) | 12 CHR<br>12 HV | [$^{11}$C]-+-PHNO | $D2^{high}$/D3 receptor availability | Striatum, thalamus, globus pallidus, substantia nigra | - | |
| Abi-dargham *et al.* 2004(146) | 13 Scztyp<br>13 HV | [$^{123}$I]IBZM | Amphetamine induced dopamine release | Striatum | ↑ (0.93) | |
| Soliman *et al.* 2008(76)[b] | 16 Scztyp<br>10 HV | [$^{11}$C] raclopride | MIST induced dopamine release | Ventral striatum | ↑ | |

↑: significantly higher in patient group; ↓: significantly lower level in patient group; -: no significant difference. [123I]IBZM: [123I](S)-(-)-3-iodo-2-hydroxy-6-methoxy-N- [(1-ethyl-2-pyrrolidinyl)methyl]benzamide; [11C]-+-PHNO: [11C]-(+)-4-propyl-9-hydroxynaphthoxazine; [18F]- DOPA: 6-[18F]fluoro-L-Dihydroxyphenylalanine; DA: dopamine; MIST: Montreal Imaging Stress Task; D1, D2, D3: Dopamine receptor sub-type 1, 2 and 3 respectively; HC: healthy control; Scztyp: Schizotypal; UHR: Clincial high risk for psychosis.

[a] Synthesis capacity increased only in subgroup that transitioned to psychosis (n=9).

[b] MIST leads to significant decrease in tracer binding in subgroup characterised as 'potential schizotype' on the basis that subjects scored >1.95 SD on the negative subscale of Chapman schizotypy questionnaire.

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**Table 2**

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 (147) | 8 GHR<br>10 HV | Siblings of patients with schizophrenia | [$^{11}$C]raclopride | 2DG induced dopamine release | Whole striatum.<br>*GHR show greater asymmetry between L/R striatum. No differences in DA release in ventral striatum* | ↓ |
| Huttunen et al. 2008 (89) | 17 $G^{HR}$<br>17 HV | 1st degree relatives of patients with schizophrenia | [$^{18}$F]-DOPA | Dopamine synthesis capacity | Caudate and putamen<br>*No differences observed in ventral striatum* | ↑ |
| Shotbolt et al. 2011 (88) | 6 GHR<br>20 HV | Co-twins of patients with schizophrenia | [$^{18}$F]-DOPA | Dopamine synthesis capacity | Whole striatum | - |
| Hirvonen et al. 2005 (91) | 6 MZ, 5 DZ, 14 HV | Co-twins of patients with schizophrenia | [$^{11}$C]raclopride | D2/3 receptor density | Caudate<br>*No differences observed in putamen or thalamus* | ↑ (0.85) |
| Hirvonen et al. 2006a (90) | 6 MZ, 5 DZ, 13 HV | Co-twins of patients with schizophrenia | [11C]SCH 23390 | D1 receptor density | mPFC, STG and angular gyrus | ↑ |
| Hirvonen et al. 2006b (148) | 6 MZ, 5 DZ, 13 HV | Co-Twins of patients with schizophrenia | [11C]SCH 23390, [$^{11}$C]raclopride | D1:D2/3 ratio | Caudate and putamen | - |
| Lee et al. 2008 (92) | 11 GHR<br>11 HV | 1$^{st}$ and 2$^{nd}$ degree relatives of patients with schizophrenia | [$^{11}$C]raclopride | Striatal D2/3 receptor density | Caudate and putamen.<br>*GHR show↓ asymmetry of receptor density in putamen* | - |

2DG: 2-Deoxy-D-glucose; DA: dopamine; DZ: Dizygotic; GHR: Genetic high risk; mPFC: Medial prefrontal cortex; MZ: monozygotic; STG: superior temporal gyrus.

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**Table 3**

PET studies of the effects of acute and chronic stress on the dopaminergic system

| Study | Population | Radiotracer | Findings |
|---|---|---|---|
| Nagano-Saito et al., 2013 (67) | 11 HV | [18F]-Fallypride<br>MIST | Stress induces displacement in dmPFC, vmPFC, PCG (15.87%), thalamus, L caudate, R putamen. No displacement observed in amygdala or ventral striatum |
| Lataster et al., 2011 (66) | 12 HV. | [18F]-Fallypride<br>MIST | Stress induces displacement in PFC. vmPFC DA release associated with subjectively rated stress. Extent of cortical release correlates with childhood adversity (68). |
| Hernaus et al., 2015b (71) | 12 HV. 12 NAPD | [18F]-Fallypride<br>MIST | NAPD show non-significantly ↓ stress induced displacement in mPFC (d=0.31). |
| Lataster et al., 2014 (69) | 11 HV. 14 relatives | [18F]-Fallypride<br>MIST | Relatives show ↓ proportion of voxels with displacement in mPFC (non significant. d=0.46). Relatives showed association between increased stress and decreased displacement (controls showed opposite). |
| Mizrahi et al., 2012(28) | 10 FEP<br>12 HV<br>12 CHR | PHNO<br>MIST | DA release greatest for FEP, then CHR (in assoc striatum). No increased release for HV. Whole–striatum - CHR>HV (d = 0.98). Limbic striatum (0.65). |
| Pruessner et al., 2004 (73) | 5 Childhood hi-stress<br>5 Childhood low-stress | Raclopride<br>MIST | Childhood high stress group show significantly ↑ventral striatal displacement compared to low stress group. |
| Oswald et al., 2014 (74) | 28 HV | Raclopride<br>AMPH challenge | Past traumatic events and perceived stress associated with greater ventral striatal DA release |
| Egerton et al., 2016 (72) | 20 HV<br>47 CHR | [$^{18}$F]-DOPA | Physical and sexual abuse, and unstable family arrangements associated with increased dopamine synthesis capacity. |

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 – non affective psychotic disorder; PCG – precentral gyrus; vmPFC – ventromedial prefrontal cortex

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**Table 4**

Genes related to dopaminergic functioning, schizophrenia and stress

| Gene | Function | Relationship to dopamine, stress and schizophrenia |
|---|---|---|
| Akt1 Akt 3 | Serine threonine kinases involved in post synaptic dopaminergic neurotransmission. | Changes in post synaptic signal transduction could lead to hypersensitivity to dopamine and alter presynaptic feedback. AKT1 has been linked to Scz in two studies (82; 83). While AKT3 has been implicated in GWAS. |
| BDNF | 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 associate with greater stress induced paranoia. |
| COMT | Catabolises 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. |
| DISC1 | Participates in a wide range of cell functions. Involved in regulation presynaptic dopaminergic function. Also involved in anchoring PDE4A to spine apparatus. | Animal models demonstrate DIC1 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 behaviour abnormalities only in mice with DISC1 mutations. Linked to Scz in multiple studies. |
| DRD2 | Dopamine receptor 2 | Changes in pre and postsynaptic receptor density or function may have marked effects on dopaminergic signalling. SNP has been associated with greater stress induced DA release. Animal study demonstrated a certain SNP is associated with increased D2R density in the nucleus accumbens following maternal deprivation. Locus associated in schizophrenia GWAS. |
| PDE4A | Involved in in a variety of responses to extracellular signals. | Together with DISC1 involved in modulation of stress signalling pathways, impairment leads to disinhibition of the stress response and PFC impairment. Has been linked to schizophrenia. |