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Schizophrenia: an integrated sociodevelopmental-cognitive model

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Abstract

Schizophrenia remains a major burden[1]. The dopamine (DA) and neurodevelopmental hypotheses attempt to explain the pathogenic mechanisms and origins of the disorder respectively[2-4]. Recently an alternative, the cognitive model, has gained popularity[5]. However the first two theories have not been satisfactorily integrated, and the most influential iteration of the cognitive model makes no mention of DA, neurodevelopment, or indeed the brain[5]. Here we show that developmental alterations secondary to variant genes, early hazards to the brain and childhood adversity, sensitise the DA system, and result in excessive presynaptic DA synthesis and DA release. Social adversity biases the cognitive schema that the individual uses to interpret experiences towards paranoid interpretations. Subsequent stress results in dysregulated DA release, causing the misattribution of salience to stimuli, which are then misinterpreted by the biased cognitive processes. The resulting paranoia and hallucinations in turn cause further stress, and eventually repeated DA dysregulation hard-wires the psychotic beliefs. Finally we consider the implications of this model for understanding and treating schizophrenia.

Schizophrenia: no longer a mystery, merely a puzzle

Schizophrenia affects about 1% of the population, and is one of the top ten causes of health burden in the World[1]. The clinical presentation is characterised by psychotic (positive) and negative symptoms, and cognitive impairments (see box 1 for further details). People who develop schizophrenia tend to show subtle cognitive, social and motor impairments in childhood. This is followed, in adolescence/early adulthood, by anxiety, low mood and social withdrawal, and then the emergence of prodromal symptoms of psychosis leading to the onset of the first psychotic episode (figure 1). Schizophrenia frequently follows a fluctuating course with enduring residual positive and negative symptoms interspersed by acute exacerbations of positive symptoms. Antipsychotics, the main pharmacological treatment, are effective at treating psychosis and reducing the risk of relapse but largely fail to treat other aspects of the disorder and have troubling side-effects[6]. There has been little progress in developing alternatives, and, unfortunately, all current antipsychotics essentially use the same mechanism as drugs discovered in the 1950s[7]. This highlights the importance of understanding the pathogenesis of the disorder. Fortunately, understanding of schizophrenia has advanced from earlier data free, stigmatising theories such as the idea that

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bad parenting caused the disorder (the 'schizophrenogenic mother'[8]). It has become clear that dopaminergic and neurodevelopmental alterations, and biases in thinking and in appraising experiences underlie the disorder. Here we review how recent advances help us to at last understand the onset and course of schizophrenia.

Dopamine dysfunction in schizophrenia (box 2)

The DA hypothesis was built on the findings that antipsychotics work by blocking DA D2/3 receptors, and that drugs that activate the DA system such as amphetamine can induce psychotic symptoms [7, 9-11]. However, meta-analysis of over 50 molecular imaging studies of the DA system in schizophrenia has now shown that the alterations in D2/3 receptor availability are inconsistent and small at most [12], whilst there is no difference in transporter availability [12, 13]. In contrast, meta-analysis has found robust evidence for elevated DA synthesis capacity, increased DA release and indeed increased baseline synaptic DA levels in schizophrenia, all with large effect sizes (cohen's d>0.8) [12]. In short, molecular imaging pin-points presynaptic dysregulation as the major locus of DA dysfunction in the disorder[7, 12, 14].

The specificity of dopaminergic dysfunction to schizophrenia and its link to psychosis

The presynaptic DA abnormality is not simply a non-specific mark of psychiatric illness - DA synthesis capacity and DA release are not elevated in people with other common psychiatric disorders[15]- and even has potential as a diagnostic test for schizophrenia[16]. However, elevated DA synthesis capacity has been reported in people with psychosis linked to temporal lobe epilepsy[17]; furthermore, individuals with schizotypal personality disorder, who have psychotic-like symptoms (and an increased risk of developing schizophrenia[18]), show both increased amphetamine-induced DA release relative to controls[19], and increased DA synthesis capacity[20].

The onset of schizophrenia is frequently preceded by a prodromal phase of sub-clinical psychotic symptoms. People who present with these "at risk" features have, on average, increased DA synthesis capacity[21, 22] but, of course, not all "at risk" individuals are truly prodromal. Elevated dopamine synthesis capacity is specific to those who go on to develop frank psychosis[20]. Furthermore, greater DA synthesis capacity is associated with greater severity of sub-clinical symptoms but again only in those who go on to develop clinical psychosis - there is no relationship between DA synthesis capacity and symptoms in those who do not develop a psychotic disorder[20]. Many of the latter group continue to experience sub-clinical psychotic symptoms. In this respect, they are similar to people in the general population who experience sub-clinical psychotic symptoms for many years without either developing a psychotic disorder or showing DA elevation[23, 24]. Another group in whom sub-clinical psychotic symptoms are seen is relatives of people with schizophrenia, but here the findings are contradictory[25, 26].

Studies using radiotracers selective for DA D2/3 receptors to index DA release following amphetamine in patients with schizophrenia indicate that greater release is associated with

greater induction of psychotic symptoms[27]. The opposite also holds: greater depletion of DA levels following inhibition of DA synthesis is associated with greater reduction in psychotic symptoms[28]. DA release is greater in patients who are acutely psychotic than in stable, remitted patients[27]. Furthermore, a longitudinal study where patients were scanned in the prodrome and then again after they developed acute psychosis, found an increase in DA synthesis capacity during the progression from the prodrome to the first psychotic episode[29].

These findings indicate a link between greater DA dysfunction and the development of more severe psychotic symptoms, and suggest that the DA dysfunction is dynamic, increasing with the worsening of the disorder. However, whilst DA dysfunction appears most marked in acute psychosis, it is not confined to schizophrenia per se, but is also seen in people with other psychotic disorders (box 2) and people with sub-clinical psychotic symptoms.

The neurodevelopmental hypothesis (box 3)

When the neurodevelopmental hypothesis was first articulated, it was based on three main lines of evidence[3, 4]. First there were the associations between pre- and peri-natal hazards on the one hand, and later schizophrenia on the other. Second, there was an excess of neuromotor, minor physical, and other markers of developmental deviance in children destined to develop schizophrenia. Third, imaging studies showed that structural brain defects were present at onset of schizophrenia, whilst post-mortem studies showed no evidence of neurodegeneration.

Since then much more evidence has accrued supporting these associations. Thus obstetric complications, such as low birth weight, Caesarean-section, hypoxia and other perinatal hazards, are linked to increased risk of schizophrenia, as is prenatal exposure to infection[30-32]. Those children who develop schizophrenia not only show an excess of markers of disordered neurodevelopment[33], but also of neurological, cognitive and social problems, all with at least moderate effect sizes (odds ratios of 2 or more[34, 35]). The evidence for structural brain alterations at onset of psychosis has continued to amass[36, 37], and there is now also evidence that it is present prior to the onset of schizophrenia [38, 39].

Weinberger originally highlighted the role of the dorsolateral prefrontal cortex[4]. Although this cortical lesion was postulated to be present from early neurodevelopment, its effects were thought to only become ***clinically*** apparent as a result of normal adolescent maturational changes combining to result in subcortical disinhibition[3, 4]. The cognitive impairments and negative symptoms seen in schizophrenia were accounted for by the cortical deficits, whilst the subcortical disinhibition, beginning in adolescence, caused the emergence of positive symptoms. Dopamine dysfunction was regarded as a manifestation of the subcortical hyperfunction and was considered as secondary to the interaction between the primary cortical lesion and normal maturational processes[3, 4]. However, several new lines of evidence, discussed below, have emerged that redefine the nature of the link between the neurodevelopmental damage and dopaminergic dysfunction.

The effect of developmental insults on the dopaminergic system

Early developmental insults to rodents have effects that mirror the changes seen in schizophrenia. Thus animals exposed to inflammatory challenges *in utero* show increased striatal levels of DA and its metabolites, and increased levels of DA synthetic enzymes in adulthood[40]. They also demonstrate increased behavioural responses to amphetamine[41], another indicator of greater DA release. Perinatal hypoxia models increase brain DA synthesis capacity, and DA levels[42, 43], while Caesarean-section is also associated with increased DA levels[44], enhanced DA release[45] and increased DA synthesis capacity in response to stress[42]. Other studies have targeted the ventral hippocampus[46] as neonatal hypoxia has been frequently associated with damage to the hippocampus in both healthy humans and in schizophrenia[47]. These studies also show increased striatal DA levels and DA release[46], increased behavioural responses to amphetamine[48], and a greater DA response to stress[49].

The effects of developmental insults are evident despite cross-fostering, indicating they are not due to the mother maltreating offspring as a result of the *in utero* exposure or post-natal influences[42, 44]. A key element is that these dopaminergic changes persist into adulthood[40]; indeed, in some models the altered dopaminergic function only becomes evident later in development[46].

Social risk factors

In recent years, evidence for the effects of social factors on schizophrenia has become well-established. Thus, being an immigrant is associated with a relative risk of 2.9 and a risk of over 4 if the migrant lives in an area where he/she is readily identifiable as being in the minority[50]. Similarly having grown up in a city, is associated with increased risk (pooled odds ratio of 1.9)[51]. Childhood adversity -such as loss of a parent, or abuse- is also associated with an increased risk of schizophrenia with an odds ratio of 2.8[52]. Whilst it is easy to see that childhood adversity, or being part of a minority group exposed to discrimination could have long-term effects on an individual's stress response, the effect of urbanicity is less obvious. However, a recent study in healthy volunteers found that city-living was associated with greater brain responses to a stress task, suggesting (although not proving) that city-living could alter the brain response to stress[53]. These findings have led to the original neurodevelopmental hypothesis being extended to include social stressors[54-56]. Furthermore, new real-time sampling techniques have demonstrated that patients with schizophrenia show greater sensitivity to everyday life hassles than controls and have linked even mild stress to increases in psychotic symptoms[57]. Similarly, higher cortisol levels have been linked to a greater likelihood of going on to develop psychosis in people at risk of schizophrenia[58], although this should be considered preliminary given the relatively modest sample sizes in studies to date.

The effects of social stressors on striatal dopamine

Social isolation is well-established as a chronic stressor in social animals. Isolation rearing leads to increased striatal synaptic DA levels in adult animals, and increased striatal DA release to subsequent environmental and drug challenges, including cocaine and

amphetamine, as adults[59]. Interestingly, position in the social hierarchy influences the recovery of the DA system after isolated animals are returned to the social group: dominant, but not sub-ordinant, monkeys show reversal of the striatal DA changes[60]. Acute stressors have also been found to activate dopaminergic transmission in the striatum in rodent models resulting in DA release and increased DA synthesis[61, 62]. Whilst many of these studies have used physical stressors such as tail-pinches or electric shocks, which have less obvious parallels with what patients experience, increased DA release is also seen to social stressors[63, 64]. For example, social instability, produced by repeatedly switching cage partners, and social defeat, where an animal loses an interaction with an aggressive animal, are associated with elevated sensitivity to amphetamine, increased striatal DA release and increased DA neuron firing[65].

Stress also increases striatal DA release in humans[66, 67], although not in all studies[68]. This inconsistency may reflect the severity of the stressor - animal studies indicate that mild stressors do not always increase striatal DA levels. Furthermore, greater DA release is associated with greater cortisol response to a challenge[66]. For obvious reasons, it is not possible to isolate children to determine if this has lasting effects on the DA system, but healthy adults who report low maternal care as children show increased DA release to a social stressor[69]. This same psychosocial stress test has been used in patients with schizophrenia and individuals at ultra-high risk of psychosis[70]. Both groups showed greater DA release to social stress than matched controls, providing evidence that people with schizophrenia, and those at risk of it, show an enhanced dopaminergic response to psychosocial stress.

The sensitivity, and sensitisation, of the dopamine system

The effects of neurodevelopmental insults on different neurotransmitter systems have been compared. Caesarean-section and mild hypoxia both affect the dopaminergic but not the serotonergic system[42] ; indeed, whilst caesarean-section increases DA levels, it decreases norepinephrine levels, at least in male rats[44]. Furthermore, although dexamethasone exposure *in utero*, a prenatal stress model, increases both brain serotonin and DA levels, the effect is more marked for the DA system[71]. Similarly isolation rearing is associated with increased DA release but reduced serotonin release to subsequent challenges[72].

An additional factor is sensitisation - the marked amplification in a response after repeated stimulation that persists over time. The DA system shows sensitisation to a number of drugs and stressors[73, 74]**.** Furthermore prior exposure to one challenge leads to an elevated subsequent dopaminergic response to a different challenge - there is cross-sensitization[75-77]. Thus animals exposed to an inflammatory challenge in utero also show a greater sensitization to repeated amphetamine administration than control animals[41]. Similarly, adult rats who had been subject to transient perinatal anoxia show greater sensitisation to the effects of subsequent stress on dopamine release in the striatum, and greater amphetamine-induced locomotor activity[45]. Cross-sensitisation has also been seen with adult rats who had been previously subject to social isolation[78], and has also been found in humans[79].

Overall, whilst environmental insults can affect a number of neurotransmitter systems, the DA system seems to be particularly sensitive to them, and furthermore its capacity for cross-sensitization means that insults may have additive, or even multiplicative, effects. Strikingly, DA sensitization in healthy controls reproduces the altered striatal and cortical responses during a cognitive task that are seen in schizophrenia[80].

Genes, neurodevelopment and the dopamine system

We have barely mentioned genes until now, a surprising omission for a disorder in which the majority of the variance is considered genetic. Dopamine related genes have also been much studied in schizophrenia, particularly the genes for dopamine receptors and for Catechol-O-Methyl -Transferase (COMT), a key enzyme that degrades DA, but effects have not been large and there are many inconsistencies[81]. This is not surprising given the imaging studies we reviewed earlier, which showed little or no abnormality in DA receptor or transporter availability, and instead located the major abnormality in presynaptic DA synthesis and release capacity. Unfortunately, there has been less research into genes involved in the synthesis and regulation of presynaptic DA (see[82] and http://www.szgene.org/). However, we should probably not expect big main effects even here given that presynaptic DA function shows relatively low heritability and a high contribution from unique environmental factors[83]. It is important to note that the high heritability of schizophrenia includes gene-environment interactions; failure to account for this may have contributed to some of the inconsistencies in the genetic studies of schizophrenia.

From the beginning, neurodevelopmental impairment in schizophrenia was considered to reflect not only environmental but also genetic risk. Indeed, an early paper was entitled “The genetics of schizophrenia is the genetics of neurodevelopment”[84]. Subsequently, it has become clear that this is true, though only in part. A number of the susceptibility genes for the disorder for which the best evidence exists are involved in neurodevelopmental processes (e.g. neuregulin1, DISC1, TCF4, *mir137*, neurogranin, neurexin1)[85-90]. Most convincingly, an excess of copy number variants (CNVs) has been repeatedly demonstrated in schizophrenia and some of the same copy number variants have been implicated in other neurodevelopmental conditions such as autism, epilepsy and learning disability[88, 91-94]. Owen *et al* (2011) point out that all these disorders are also subject to early environmental hazards and suggest that together they constitute a continuum of neurodevelopmental causality[95].

Preclinical evidence indicates that altered function in a number of these genes perturbs the DA system. For example, DISC1 knock-down mice showed an increased behavioural response, and increased striatal DA release, to methamphetamine[96]. Alterations in neuregulin1 and dysbindin have also been found to impact on the DA system. For example, neonatal administration of neuregulin1 resulted in increased striatal tyrosine hydroxylase levels and activity and increased DA levels[97], while dysbindin mutant mice showed hyperactivity to DA agonists[98]. TCF4, a transcription factor, also impacts on the DA system by activating tyrosine hydroxylase transcription[99]. Finally, further support for the idea that disrupted neurodevelopment and dopaminergic dysfunction combine to underlie psychosis is provided by the 22q11.2 deletion syndrome, a large CNV that includes COMT and

developmental genes and is associated with neurodevelopmental abnormalities and a ~25 fold increased risk of schizophrenia[91].

Post-synaptic dopamine signalling

We have focused on presynaptic DA but we cannot exclude a role for post-synaptic DA signalling. Indeed a recent finding in patients with both schizophrenia and substance dependence highlights the potential role of post-synaptic DA signal transduction[100]. In contrast with previous findings in schizophrenia, this study found reduced DA release to amphetamine; but, nevertheless, DA release was still positively associated with the induction of psychotic symptoms[101]. This suggests that post-synaptic hypersensitivity to DA may contribute to psychosis. In support of a role for post-synaptic factors, schizophrenia is associated with gene variants and altered expression of proteins involved in post-synaptic DA signal transduction, such as AKT1, GSK-3β and DARPP-32[102-104]. Preclinical studies indicate that alterations in these pathways can dramatically alter DA-related function. For example, an increased behavioural response to amphetamine is seen with genetic or pharmacological manipulations that increase GSK-3 β function or those that reduce AKT1 function[105, 106]. Furthermore DARPP-32 knockout mice show altered behavioural responses to amphetamine and increased sensitisation to cocaine[107, 108]. It is important to note that DA sensitisation involves post-synaptic as well as presynaptic changes[109].

Thus alterations in these post-synaptic factors could result in a pathologically increased post-synaptic response to DA which may underlie psychosis in dual diagnosis patients, but could also contribute to psychosis in others by amplifying the effects of presynaptic DA dysfunction due to interactions with environmental risk factors. There is already some evidence of such gene-environment interactions; for example SNPs in AKT1 have been found to show an interaction with two of the environmental risk factors that alter presynaptic DA function, obstetric complications and cannabis, to increase the risk of psychosis[110-112].

Cognitive theories and their link to dopaminergic dysfunction

Together the DA and developmental hypotheses explain much of what we know concerning the biology of psychosis. However, they do little to help us understand the symptoms that patients suffer. The last decade has seen the rise of cognitive models which attempt to do this[5, 113]. These suggest that exposure to social adversities (e.g. child abuse, intrusive life events) bias an individual towards developing cognitive schemas that see the world as threatening, and to attributing negative events and experiences to external factors (such as other people)[113]. In such models, stress is seen as resulting in anomalies of conscious experience which trigger a search for an explanation. Then biased cognitive schema and appraisal processes result in the erroneous judgement that these puzzling experiences are externally driven and uncontrollable - in this way, paranoid delusions are postulated to develop.

Cognitive models were initially almost wholly “brainless” but have now begun to take note of biological theories[5, 114]. Research highlighting the importance of DA signalling in the salience of stimuli has been crucial to this. DA dysregulation is seen as resulting in aberrant assignment of salience to stimuli, and it is the cognitive interpretation of these excessively

salient stimuli that results in psychotic symptoms[2, 115]. Thus environmental adversity acts both to dysregulate the DA system and to form biased cognitive schema. The biased schema, in turn, result in the excessively salient stimuli being interpreted as threatening. It is easy to see how this can lead to paranoid interpretations. The net result is additional stress, and further DA dysregulation - a vicious cycle that is likely, given the central role of the striatum and dopamine in habit formation, to result in paranoid ideas becoming fixed - effectively hard-wired[116].

In earlier versions of the DA hypothesis, it was not clear how DA dysfunction accounted for hallucinations[2]. However, recent studies in primates indicate that as well as coding the saliency of external stimuli, midbrain DA activity also codes the uncertainty around subjective perceptual decisions about the detection of stimuli[117, 118]. Importantly this is independent of actual stimulus detection[117]. Thus DA dysregulation could impair the subjective discrimination of internal from external stimuli, leading to the misattribution of internal stimuli as arising externally. In support of this, patients with schizophrenia show impairments in the ability to detect stimuli and in the normal attenuation of cortical responses to self-made percepts[119-122]. The failure to attenuate the salience of self-made percepts could also result in the misattribution of their agency, and so account for passivity delusions. The signalling of salience by dopamine plays an important role in reward learning by encoding information about the mismatch between what is expected following a stimulus and what actually happens- the precision of prediction errors in computational models [123]. By disrupting reward learning in this way, DA dysregulation could also account for amotivation, apathy and other negative symptoms of schizophrenia. Supporting this, even relatively modest increases in dopaminergic neurotransmission in rodents disrupt reward learning and decrease willingness to work for reward (see review[124]).

From state to trait: an integrated sociodevelopmental model

Our model combines aspects of the dopamine, neurodevelopmental and sociodevelopmental hypotheses with cognitive theories. Firstly, developmental deviance secondary to variant genes, hazards to the brain and social adversity in childhood, disrupts the development and sensitises the DA system (figure 2). At the same time social adversity also biases the cognitive schema that the individual uses to interpret experiences, towards psychotic interpretations. Subsequent stress then results in dysregulated DA release, leading to the aberrant assignment of salience, which, when interpreted in the context of biased cognitive schema, contributes to further stress. A vicious cycle is established with stress increasing DA dysregulation, which leads to more stress and so further DA release which eventually hard-wires the psychotic interpretation (figure 3). There is a progressive dysregulation of DA seen from the prodrome to the first and subsequent psychotic episodes.

This is a dynamic model in that the degree of dopaminergic dysfunction fluctuates in response to the psychological response to the abnormal DA signalling. This contrasts with previous static versions of the DA hypothesis which could not account for relapses and remissions of the illness. Thus, the DA dysregulation reduces after the acute stressor(s) abate(s), although it does not normalise completely in most patients. This explains a) why some 10% of patients experience no further episodes of psychosis after the first episode[125],

but also b) why people who have experienced a psychotic episode remain at risk of further episodes even years later and c) the role of social stress in relapse[125]. Finally, given dopamine's role in reward learning, the enduring DA dysfunction could account for the negative symptoms that many patients experience between acute episodes.

A key line of evidence for the original neurodevelopmental hypothesis was that premorbid motor and intellectual abnormalities were evident in pre-schizophrenic children[34]. At the time it was thought that the dopaminergic dysfunction was mesolimbic rather nigrostriatal. However, subsequent findings indicate that the dopaminergic dysfunction includes the motor and associative parts of the striatum[12] , and abnormalities in the latter have been linked to poorer cognitive function in people with prodromal signs of schizophrenia[21]. Thus motor and cognitive abnormalities could be accounted for by the effect of altered dopaminergic function in the motor and associative striatum respectively. Supporting this, transgenic mouse models show that even a relatively subtle increase in striatal dopaminergic neurotransmission impairs cognitive function[126]. Of course, our model does not preclude developmental disruption of other systems - this could both contribute to cognitive dysfunction, and underlie the greater sensitivity of the dopaminergic system to subsequent stressors[46, 127]. Some, albeit tentative, support for this comes from the finding that smaller grey matter volumes are associated with a greater stress-induced increase in a peripheral marker of DA[128]. Similarly, it is likely that individuals with greater exposure to risk factors, and particularly greater severity of developmental insult, will show more marked dopaminergic dysregulation but also dysfunction of other systems. This explains why patients with more risk factors tend to have a poorer prognosis[129], and accounts for heterogeneity in the cognitive impairments seen in patients with schizophrenia[130].

The model explains the overlap both in risk factors and brain abnormalities between schizophrenia and neuropsychiatric conditions such as autism and epilepsy as they share neurodevelopmental origins[131-133]. However, it proposes that it is the impact of these developmental factors and subsequent social stressors on the DA system that determines whether the trajectory is towards progressive dopamine dysregulation, and psychosis, or, where the dopamine system is not progressively dysregulated, another diagnosis or no disorder. Finally it is primarily a theory about psychosis in schizophrenia, and putatively, psychosis in other conditions. Thus, it would account, for example, for the higher rates of psychosis in conditions such as epilepsy, learning disability and autism with similar neurodevelopmental origins.

Strengths and Limitations

The evidence linking neurodevelopmental and sociodevelopmental risk factors to schizophrenia, and for presynaptic DA dysfunction in the disorder, is supported by meta-analyses (see boxes 2 and 3). Similarly the link between developmental risk factors to altered DA function is supported by a large number of preclinical studies. As such it would take a substantial amount of new evidence to refute these aspects of the model. However, the link between the environmental risk factors and DA dysfunction is less well established, particularly in humans, as is the proposal that the DA changes are dynamic - both these components are reliant on a small number of studies and thus warrant further testing.

Similarly, whilst the finding that people with schizophrenia show biased cognitive schemas has been replicated in at least two other studies, this is far from established, and evidence to support our proposal that these are biased prior to the onset of psychosis and a consequence of social adversity is needed. The evidence for dopamine's role in encoding subjective sensory discrimination and that patients show disrupted sensory discrimination is also limited to a handful of studies.

We have not discussed some of the risk factors and neurobiological alterations associated with schizophrenia where more evidence is needed. Some, such as the progressive structural brain loss seen in some patients, may be accounted for within our model by the effects of stress and/or antipsychotic treatment[134, 135], or be non-specific correlates of neurodevelopmental disruption. Others may emerge in the fullness of time as key upstream regulators of the dopamine dysfunction. Amongst these, glutamatergic abnormalities, although not always consistent[136], have attracted considerable recent interest. Glutamatergic hypofunction could contribute to dopaminergic dysfunction[137], although this remains to be determined in patients. The influence of another factor, oestrogens, could explain the later peak age of onset in women, but, whilst estrogens are clearly involved in regulating DA function in preclinical models[138], this has yet to be established in humans. Similarly, whilst our model accounts for the link between stimulant use and increased risk of schizophrenia as these drugs are known to induce dopamine sensitisation[79], there continues to be some uncertainty over whether abuse of other psychotogenic drugs, such as ketamine and cannabis, operate via dopaminergic pathways[139]. Finally, whilst the dynamic nature of the proposed DA dysfunction accounts for the fluctuating course of the acute psychotic phases of schizophrenia, the evidence is less clear on how it accounts for the persisting negative symptoms and deficit state that generally persist between acute episodes.

Implications and future directions

This model draws on a number of previous theories[4, 55, 101, 140-142], and is likely to be refined with further testing. There are several areas where more evidence may be particularly informative. One is the developmental trajectory of DA function in experimental models of schizophrenia, beginning earlier than previously studied[143], and also examining the interactive effects of social risk factors. Another is the interaction between genes impacting on the dopamine system and environmental risk factors. A third is the hypothesised interaction between neurodevelopmental and later social effects on the DA system, and particularly the hypothesised dynamic change and the impact of stressors on this. A fourth is the role of cognitive schema in the transition from experiencing 'aberrant salience' to developing psychosis. We have focussed on dopamine in the striatum because this is the region most studied, but this does not preclude effects in other regions- for example, rodent studies show that stress also has effects on DA release in other brain regions[61]- and this warrants further investigation.

This model highlights that patients are not 'doomed from the womb', in contrast to some early interpretations of the neurodevelopmental hypothesis, nor to progressive deterioration. Instead it suggests that life events, and the cognitions associated with them, play a key role, and that by altering cognitive schema, and by reducing stress, psychological therapies and

social interventions may interrupt the vicious cycle which is dysregulating DA (figure 4). Evidence from an animal developmental model of schizophrenia also indicates that treatments that reduce stress responsivity prevent the emergence of DA dysregulation[144]. These interventions are likely to be particularly critical early in the illness, before there has been progressive DA dysregulation, and patterns of interpreting events become hard-wired.

We have focussed on presynaptic DAergic function but alterations in post-synaptic signal transduction may contribute to further disrupt DA signalling. Whilst further work is needed to determine if post-synaptic signalling is disrupted in schizophrenia, targeting these pathways may nevertheless be therapeutically beneficial to redress presynaptic DA dysfunction. Additionally the model indicates new upstream targets for drugs to reverse the dopamine dysregulation - such as the *gamma*-aminobutyric acid (GABA)-ergic and glutamatergic regulation of midbrain dopamine neuron firing[145-147]. Finally, the model indicates that treatment of schizophrenia needs to address psychological, sociodevelopmental and biological factors: it cannot be either wholly brainless or totally mindless.

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Box 1

Term	Explanation
Delusion	A fixed implausible, preoccupying belief, such as that a microchip has been implanted behind the ear and is controlling their thoughts
Hallucination	A voice, vision or other percept in the absence of a stimulus. In schizophrenia these characteristically take the form of voices commenting on the sufferer's actions
Passivity delusions	Delusions that an external agency is controlling thoughts, actions or perceptions
Positive symptoms	Psychotic symptoms such as delusions and hallucinations
Prediction error	Used in computational models to describe the mismatch between what is expected and what actually happens that drives learning
Psychosis	A syndrome characterised by one or more of the following symptoms: delusions, hallucinations, thought disorder, catatonia
Psychotic disorders	Schizophrenia is the most common psychotic disorder, but psychosis is also seen in bipolar and unipolar affective disorders
Negative symptoms	Symptoms such as apathy, reduced social interactions, poor self-care
Schizophrenia	A chronic mental illness characterised by persistent psychotic and negative symptoms and relatively subtle cognitive impairment.

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Box 2

Summary of evidence for the dopamine hypothesis of schizophrenia

	Dopaminergic index	Link to schizophrenia	Strength of evidence
Drug studies	Effect of DA agonist drugs (eg amphetamine)	Induces/ worsens psychotic symptoms	+
	Effect of DA receptor antagonists (eg antipsychotics)	Reduces symptoms	++
	Effect of DA depleting drugs (eg reserpine)	Reduces symptoms	+
Peripheral markers	DA metabolites in CSF and plasma	Increased in schizophrenia	~ may depend on phase of illness and influenced by peripheral catecholamine metabolism
Ex vivo studies	Dopamine and DA metabolite levels in brain	Increased in striatum in schizophrenia	+ potentially confounded by prior antipsychotic treatment
Brain imaging studies	DA synthesis and DA release capacity, and baseline DA levels	Increased in striatum in schizophrenia	++

++=found in meta-analysis; += found in well-controlled studies; ~inconsistent findings

Box 3

Summary of evidence for the neurodevelopmental hypothesis of schizophrenia

	Indicator	Link to schizophrenia	Strength of evidence
Pre or perinatal risk factors	Obstetric complications		++
	Low birth weight		++
	In utero infection		++
Developmental trajectory	Motor delay		++
	Social alterations		++
	Cognitive impairments		++
Brain structural alterations	Ventricular enlargement		++
	Grey matter reductions		++
	White matter disruption		+

++=found in meta-analysis; += found in well-controlled studies, ~inconsistent findings

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Search strategy and selection criteria

We searched Pubmed and Embase from 1966 to June 2013 and reviewed article bibliographies using the following search terms: “schizophrenia”, “psychosis”, in combination with “dopamine”, “aetiology”, “risk factors”, “cause”, “theory”, “neurodevelopmental”, and “cognitive”. Where possible we have cited meta-analyses and systematic reviews.

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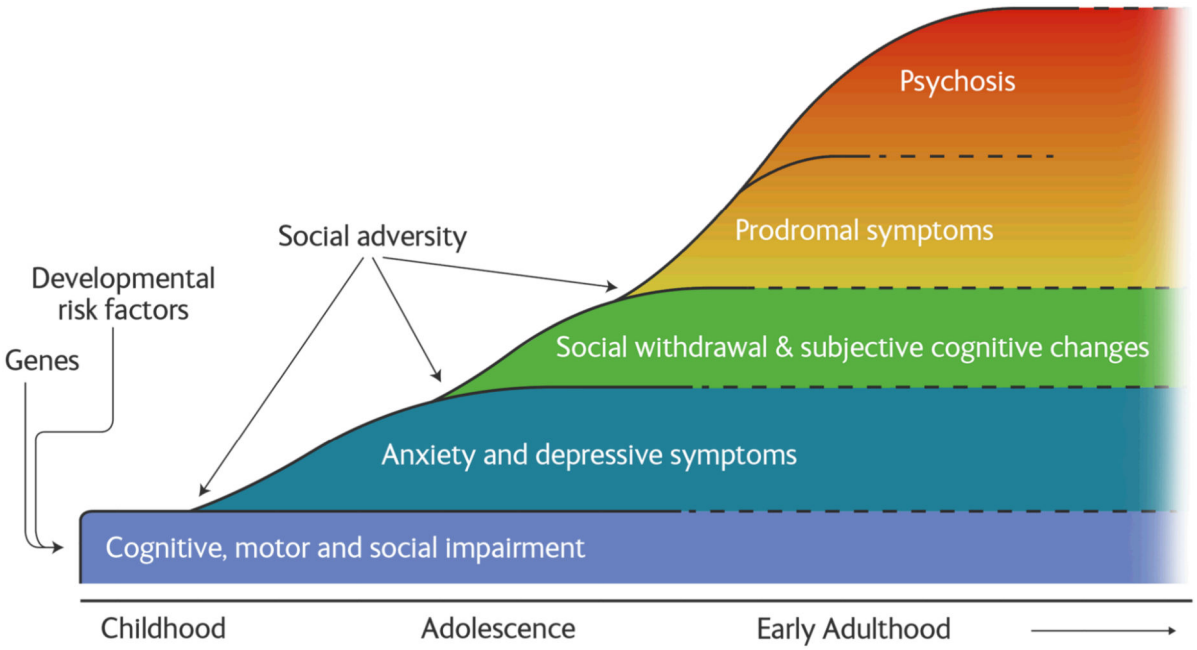

Figure 1. The trajectory to schizophrenia showing the evolution of symptoms and the main risk factors

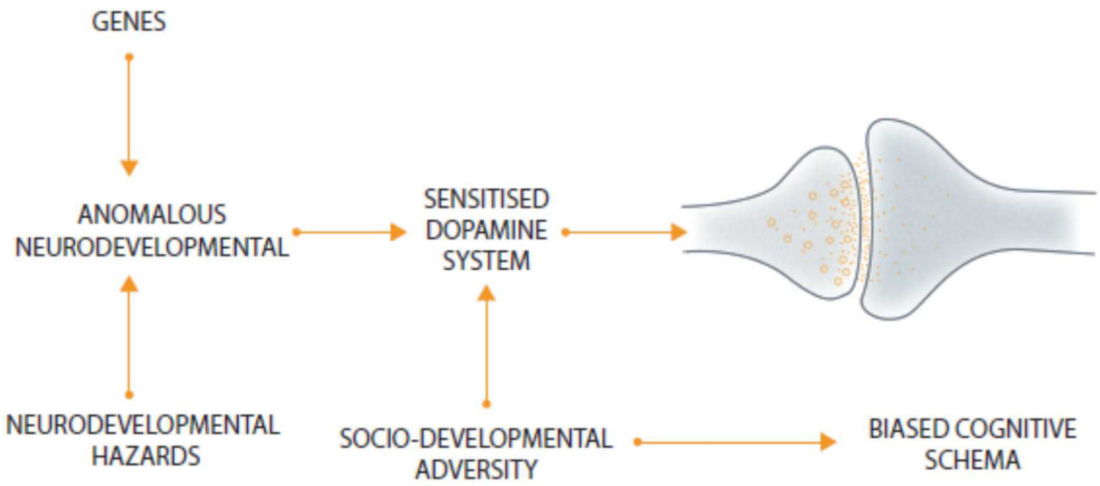

Figure 2. The effect of neurodevelopmental and sociodevelopmental risk factors for psychosis on the dopamine system and cognitive schema

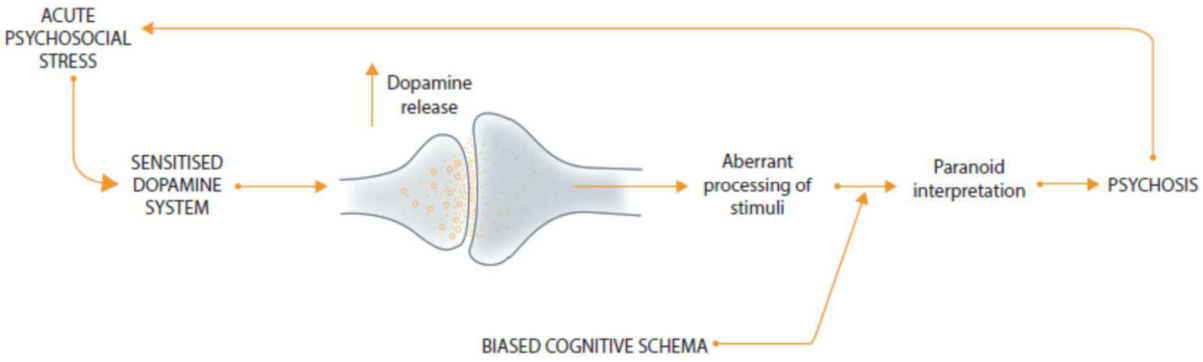

Figure 3. Model of the onset of psychosis showing the interaction between acute stress, dopamine dysfunction and biased cognitive schema

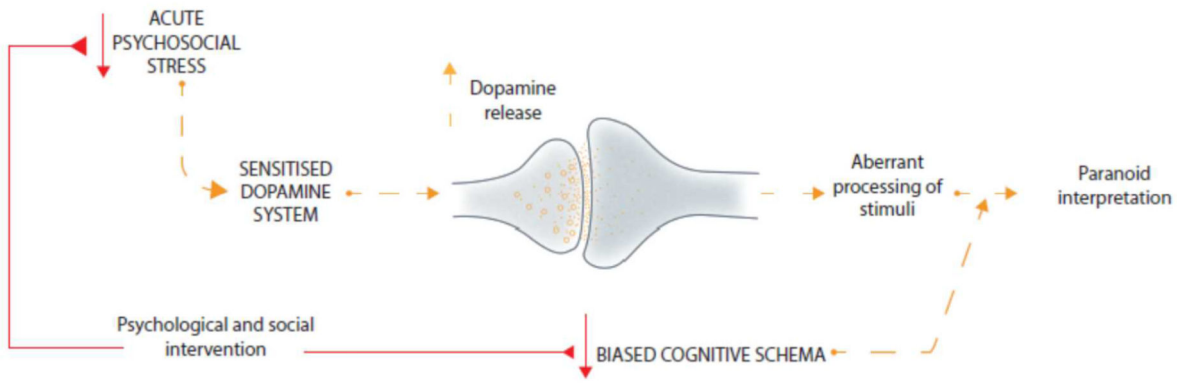

Figure 4. Sites at which psycho-social interventions may act to prevent psychosis

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