Dopamine and glutamate in schizophrenia: biology, symptoms and treatment

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Glutamate and dopamine systems play distinct roles in terms of neuronal signalling, yet both have been proposed to contribute significantly to the pathophysiology of schizophrenia. In this paper we assess research that has implicated both systems in the aetiology of this disorder. We examine evidence from post-mortem, preclinical, pharmacological and in vivo neuroimaging studies. Pharmacological and preclinical studies implicate both systems, and in vivo imaging of the dopamine system has consistently identified elevated striatal dopamine synthesis and release capacity in schizophrenia. Imaging of the glutamate system and other aspects of research on the dopamine system have produced less consistent findings, potentially due to methodological limitations and the heterogeneity of the disorder. Converging evidence indicates that genetic and environmental risk factors for schizophrenia underlie disruption of glutamatergic and dopaminergic function. However, while genetic influences may directly underlie glutamatergic dysfunction, few genetic risk variants directly implicate the dopamine system, indicating that aberrant dopamine signalling is likely to be predominantly due to other factors. We discuss the neural circuits through which the two systems interact, and how their disruption may cause psychotic symptoms. We also discuss mechanisms through which existing treatments operate, and how recent research has highlighted opportunities for the development of novel pharmacological therapies. Finally, we consider outstanding questions for the field, including what remains unknown regarding the nature of glutamate and dopamine function in schizophrenia, and what needs to be achieved to make progress in developing new treatments.

Key words: Psychosis, schizophrenia, dopamine, glutamate, antipsychotics, striatum, NMDA receptors, D2 receptors, D1 receptors, dorsolateral prefrontal cortex, GABA interneurons, amphetamine, ketamine, cognitive symptoms

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Schizophrenia is a severe mental disorder characterized by positive symptoms such as delusions and hallucinations, negative symptoms including amotivation and social withdrawal, and cognitive symptoms such as deficits in working memory and cognitive flexibility[1]. The disorder accounts for significant health care costs, and is associated with a reduced life expectancy of about 15 years on average[2].

Antipsychotics were serendipitously discovered over fifty years ago, but it took another decade or so until dopamine antagonism was demonstrated as central to their clinical effectiveness[3]. Further evidence implicating the dopamine system in the pathophysiology of schizophrenia has subsequently accumulated, and it remains the case that all licensed first-line treatments for schizophrenia operate primarily via antagonism of the dopamine D2 receptor[4].

However, despite the central role that dopamine plays in our understanding of schizophrenia, it has also become increasingly clear that dysfunction of this system may not be sufficient to explain several phenomena. In particular, dopamine blockade is not an effective treatment for negative and cognitive symptoms and, in a significant proportion of patients, it does not improve positive symptoms either. As a result, attention has turned to additional neurochemical targets. Glutamate is the major excitatory neurotransmitter of the central nervous system. The finding that antagonists of a specific glutamate receptor, the N-methyl-D-aspartate (NMDA) receptor, induce psychotic symptoms has led to a wealth of research implicating the glutamate system in the pathophysiology of schizophrenia.

In this paper we review the evidence regarding dopaminergic and glutamatergic functioning in schizophrenia. We survey indirect findings from preclinical, genetic and pharmacological studies, evidence from post-mortem research, and results of neuroimaging studies that characterize functioning in living patients. We discuss how dysregulation of these systems may lead to the symptoms of the disorder, and the therapeutic possibilities associated with their pharmacological modulation. We then explore what may underlie this dysregulation, and the interaction between the two systems, before concluding by considering outstanding questions for the field.

DOPAMINE

Dopamine was initially thought to be a biologically inactive intermediary compound on the synthetic pathway between tyrosine and noradrenaline. Work by A. Carlsson and others, however, demonstrated that dopamine depletion inhibited movement, and that this effect could be reversed following the administration of the dopamine precursor L-DOPA. This established that the molecule was of major biological importance in its own right[5], and discrete dopaminergic projections were subsequently identified.

That dopaminergic dysfunction might play a role in the development of psychotic symptoms is one of the longest standing hypotheses regarding the pathophysiology of schizophrenia. Below, we discuss the evidence for dopamine dysfunction in

schizophrenia, before considering how this may lead to psychotic symptoms, and the mechanisms through which dopamine modulating treatments exert their effects.

Indirect evidence for dopamine dysfunction in schizophrenia

Animal models

Rodent models of schizophrenia are useful for investigating molecular mechanisms that may be of pathophysiological relevance, and for testing novel therapeutic interventions.

One well characterized model of dopaminergic hyperactivity involves administering repeated doses of amphetamine. This has been shown to induce events that are also observed in individuals with schizophrenia, such as reduced prepulse inhibition, stereotyped behaviours, and impaired cognitive flexibility and attention[6]. Given that amphetamine results in dopamine release, and that the above effects can be ameliorated with the administration of dopamine antagonists, this provides indirect evidence for a role of dopamine in behaviour thought to be a proxy for psychotic symptoms.

Another example is that of mice genetically modified to overexpress dopamine D2 receptors in the striatum, which also display a wide range of schizophrenia-like behaviours[7]. Similarly, transgenic insertion of tyrosine hydroxylase and guanosine triphosphate (GTP) cyclohydrase 1 into the substantia nigra in early adolescence increases dopamine synthesis capacity, and has been associated with a schizophrenia-like behavioural phenotype[8].

Other examples do not target the dopamine system directly, but are still associated with dopaminergic abnormalities. The methylazoxymethanol acetate (MAM) model involves inducing neurodevelopmental disruption of the hippocampus via the administration of MAM to pregnant rats, and is accompanied by increased firing rates of mesostriatal dopamine neurons[9]. A model of environmental risk factors in which rats were socially isolated post weaning has also been associated with increased striatal presynaptic dopamine function[10].

In summary, multiple methods have been used to induce increased striatal dopamine signalling in animal models, and these consistently produce behaviours analogous to those observed in individuals with schizophrenia.

Cerebrospinal fluid and post-mortem studies

Studies examining levels of dopamine and its metabolites – 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) – in schizophrenia, both peripherally and in cerebrospinal fluid (CSF), have given inconsistent results[11-13]. This may be due to the fact that these levels are a state dependent marker, and to the effects of antipsychotic treatment. Studies have found that levels of dopamine, HVA and DOPAC in CSF are only increased in those receiving antipsychotic treatment[13,14], and that reductions occur following the withdrawal of antipsychotics[15,16].

Some[17-19], but not all[20], studies of HVA have found higher levels in both CSF and plasma of acutely relapsed patients compared to stable patients. There have also been suggestions that baseline plasma HVA levels may predict subsequent response to antipsychotics, which shows some parallels with imaging findings considered below[21].

This approach to studying the dopamine system, however, has declined in popularity over recent years. A major weakness is that the measurement occurs distal from the dopamine neurons of interest. Since both hypo- and hyperdopaminergic function may exist within an individual simultaneously, a technique that allows for anatomical specificity is required to understand the nature and localization of changes.

Early post-mortem investigations suggested that striatal D2 receptor levels might be raised in individuals with psychosis[22], and a meta-analysis of seven post-mortem studies suggested that receptor levels were increased with a large effect size[23]. However, no studies of antipsychotic naïve individuals exist, and the majority are of individuals chronically treated with antipsychotic medications, which have been found to lead to D2 receptor upregulation[24,25].

Post-mortem studies have also examined the substantia nigra. In these studies evidence regarding dopamine function is inconsistent, with some studies suggesting an increase in tyrosine hydroxylase levels in patients[26], but others finding no difference[27,28]. Other studies have found abnormal nuclear morphology of substantia nigra neurons[29], reduced dopamine transporter (DAT) and vesicular monoamine transporter (VMAT) gene expression, and increased monoamine oxidase A expression[28].

Recent collaborative efforts in amassing significantly larger post-mortem sample sizes, and applying more sophisticated methods of analysis, may improve our understanding in the near future[30]. However, even with these developments, the drawbacks of post-mortem studies include heterogenous tissue quality, the fact that the majority of samples are from older patients with a long history of antipsychotic use, limited information regarding clinical phenotype, and that death itself leads to a wide range of neurobiological changes that may obscure important differences.

Studies in living participants have greater potential to include younger individuals, drug-free subjects, and also the ability to look at within-individual changes in symptoms and how these relate to pharmacological manipulation.

Psychopharmacology of dopaminergic agonists and antagonists

The discovery that chlorpromazine and reserpine were effective in the treatment of schizophrenia occurred prior to the identification of dopamine as a neurotransmitter. It was not until the 1970s that the clinical potency of antipsychotics was incon-

trovertibly linked to blockade of the dopamine D2 receptor[31,32]. In addition, selective D2 antagonists show equivalent efficacy to drugs with a broad spectrum of activity[33], indicating that D2 antagonism is sufficient for antipsychotic efficacy.

It was also noted that drugs such as amphetamine that increase dopaminergic neurotransmission could induce psychotic symptoms in healthy individuals, and exacerbate psychotic symptoms in individuals with schizophrenia[34,35]. Similarly, L-DOPA treatment in Parkinson's disease has been found to induce psychotic symptoms in some individuals[36]. However, while amphetamine-induced psychosis is marked by hallucinations, delusions, paranoia, and conceptual disorganization, it is not typically associated with negative and cognitive symptoms of the same form as those observed in schizophrenia[37]. This relative specificity to positive psychotic symptoms contrasts with glutamatergic models of schizophrenia (see later).

Summary of indirect findings

The findings discussed above provide evidence that aberrant function of the dopamine system contributes to psychotic symptoms (see Table 1). However, these methods are unable to identify where within the brain this dysfunction is localized to and, for the most part, cannot provide a direct link to symptoms. We next discuss methods for in vivo imaging of the dopamine system, which has the potential to overcome these obstacles.

Imaging dopamine in vivo

Both magnetic resonance imaging (MRI) and positron emission tomography (PET) have been used to characterize the dopamine system in vivo (Table 2). PET provides molecular specificity to the dopamine system, but this comes at the cost of lower temporal and spatial resolution compared to MRI.

MRI

Although MRI lacks the ability to directly image the dopamine system, recent work imaging neuromelanin has shown some promise in quantifying the dopamine system in vivo. Neuromelanin is synthesized via iron dependent oxidation of cytosolic dopamine, and accumulates in dopamine neurons of the substantia nigra. It has been demonstrated that the neuromelanin MRI signal is associated with integrity of dopamine neurons, with dopamine release capacity in the striatum, and with the severity of psychosis in schizophrenia[49].

Functional MRI (fMRI) has also been used in attempts to infer functioning of the dopamine system. Task-based fMRI has been adopted to quantify the striatal response to reward, and this has been linked to dopamine function, although the precise relationship is complex[50]. There is consistent evidence of reduced ventral striatal activation to reward in schizophrenia[51]. We consider how this is consistent with the hypothesis of an overactive dopamine system in the section discussing psychotic symptoms below.

PET: dopamine receptors

Dopamine receptors have been studied using a wide range of radioligands. The majority of studies have used ligands specific for D2-type (i.e., D2, D3 and D4) dopamine receptors, although several studies have also examined D1-type (i.e., D1 and D5) receptors.

Table 1 Summary of indirect evidence for dysfunction of dopamine and glutamate systems in schizophrenia

	Dopamine	Glutamate
Animal models	Amphetamine administration, striatal D2 overexpression, and transgenically increased dopamine synthesis capacity are associated with schizophrenia-like behaviours. Models of neurodevelopmental and social risk factors are associated with increased striatal dopamine function.	Administration of NMDA antagonists induces a wide variety of schizophrenia-like behaviours. Genetic models that disrupt NMDA signalling (by reducing levels of D-serine, inactivating D-amino oxidase or decreasing dysbindin) show behavioural and neurobiological changes similar to those observed in schizophrenia.
Cerebrospinal fluid (CSF)	Studies of DOPAC and HVA both peripherally and in CSF have been inconsistent.	Studies of glutamate levels are inconsistent, but kynurenic acid (an NMDA antagonist) levels appear consistently raised.
Post-mortem studies	Increased D2 receptor densities have been observed, but may result from medication use.	Glutamate neurons show reduced dendrite arborization, spine density and synaptophysin expression. Glutamate transporter EAAT2 protein and mRNA levels appear reduced in frontal and temporal areas. There is some evidence that glutaminase expression is increased in patients, and also that GRIN1 abnormalities exist.
Pharmacological studies	Clinical potency of antipsychotics is strongly linked to their affinity for the D2 receptor. Amphetamines can induce positive psychotic symptoms in healthy controls and worsen symptoms in patients.	NMDA antagonists induce positive, negative and cognitive psychotic symptoms in healthy controls. Chronic ketamine users show subthreshold psychotic symptoms.

NMDA – N-methyl-D-aspartate, DOPAC – 3,4-dihydroxyphenylacetic acid, HVA – homovanillic acid, EAAT – excitatory amino acid transporter

Table 2 Summary of imaging studies of the dopamine and glutamate systems in schizophrenia

			Striatal	Extra-striatal
DOPAMINE	Dopamine receptors	D1	Few studies, and no differences consistently noted.	Studies using [^{3}H]SCH 23390 have reported decreased binding in patients; those using [^{11}C] NNC 112 reported an increase in patients.
		D2	No patient/control differences in unmedicated cohorts. Variability increased in patients.	Generally poor signal-to-noise ratio. No consistent patient/control differences.
	Presynaptic dopamine function		Consistently increased in both previously medicated and antipsychotic naïve patients (g=0.7). Patient-control differences appear greatest in the dorsal striatum.	Two studies have found increased synthesis capacity in the substantia nigra (although not observed in another). One amphetamine challenge study found reduced release in patients in prefrontal cortex. Psychological challenges have produced less clear results. Findings of challenge studies in the substantia nigra are inconsistent.
	Dopamine transport	DAT	No patient-control differences in mean binding, but variability increased in patients.	Fewer studies. Some suggestion that thalamic levels may be raised in patients.
		VMAT		Two studies have found increased levels in the ventral brainstem of patients.
GLUTAMATE	Basal ganglia		Glx (g=0.4) and glutamate (g=0.6) levels raised in patients.	
	Thalamus		Glutamine levels raised in patients (g=0.6).	
	Medial temporal lobe		Glx levels raised in patients (g=0.3).	

DAT – dopamine transporter, VMAT – vesicular monoamine transporter, Glx – glutamate + glutamine

Striatum

It has been proposed that excessive dopaminergic neurotransmission in schizophrenia results from upregulation of striatal postsynaptic D2-type receptors. However, meta-analyses of studies using PET show only a small increase in receptor density at most in schizophrenia, and there is no significant difference between patients and controls in analyses restricted to medication naïve patients[52]. When combined with evidence that antipsychotic treatment appears to lead to D2 receptor upregulation[24,25], it appears possible that any patient-control differences may be secondary to confounding by treatment.

There are caveats, however, to the above inference. First, the majority of studies are unable to measure the absolute density of receptors, because a proportion of receptors will be occupied by endogenous dopamine. If schizophrenia is associated with increased synaptic dopamine levels, this could mask a concurrent increase in receptor densities. Indeed, one study where dopamine depletion was undertaken prior to PET scanning showed significantly increased dopamine receptor availability in patients, although this increase was not significant in another study using this approach[53,54].

Second, the majority of ligands are selective for D2 over D3 and D4 receptors. The studies that have employed butyrophenone tracers (that have an affinity for D4 receptors in addition to D2 and D3 receptors) have tended to show raised receptor densities compared to those studies employing ligands that do not have D4 affinity[52]. In addition to potential differences in D2/3/4 subtype proportions, D2 receptors exist in both high and low affinity states, and some evidence suggests that schizophrenia may be associated with an increased proportion of receptors in the high affinity state[55-58].

Furthermore, following receptor internalization, some tracers remain bound, while others dissociate. So, if receptor internalization is increased in one group, this would register as reduced ligand binding if using a tracer that dissociates on internalization, but not if using a tracer that remains bound[59,60].

Finally, it has recently been shown that the *variability* of striatal D2 receptor levels is greater in patients than controls[61], suggesting that differences in D2 receptor density may exist, but only within a subgroup of patients, although whether this reflects a primary pathology or an effect of prior antipsychotic treatment in some patients remains unclear.

D1-type receptors have not been studied frequently in the striatum, and the studies that have been undertaken do not show any clear patient-control differences[52,62].

Extra-striatal regions

The measurement of dopamine receptors in extra-striatal regions is complicated by the lower receptor densities, which means

that the signal-to-noise ratio is much lower than in the striatum. Studies of thalamic, temporal cortex and substantia nigra D2/3 receptor availability have not consistently shown patient-control differences[63]. Other cortical regions have rarely been studied, and have not shown consistent changes[63].

D1 receptors have been more thoroughly examined in cortical regions than in the striatum. Two studies using [^{11}C]NNC 112 reported an increase in patients[64,65], while one reported a decrease[66]. Four studies using [^{3}H]SCH 23390 have reported a decrease[62,66-68], while two found no significant differences[69,70]. The interpretation of these findings is complicated by the fact that dopamine depletion paradoxically decreases the binding of [^{3}H]SCH 23390, while it has no effect upon [^{11}C]NNC 112 binding. Furthermore, antipsychotic exposure decreases D1 receptor expression, and both the above ligands also show affinity for the 5-HT$_{2A}$ receptor[71-73].

PET: dopamine transport mechanisms

DAT is involved in reuptake of dopamine from the synaptic cleft, and is often interpreted in PET studies as a measure of the density of dopamine neurons. Studies examining DAT density in the striatum have found no consistent differences between patients and controls[52], although, as with D2 receptors, variability is increased in schizophrenia, suggesting that differences may exist within a subgroup[61]. A more recent study did find significantly raised striatal DAT levels in patients, but this was observed in those with a chronic illness with long-term antipsychotic exposure[74].

There have been fewer studies examining extra-striatal regions, although the ones that have been undertaken do suggest that thalamic DAT levels may be raised in patients[74,75].

VMAT2 transports intracellular monoamines into synaptic vesicles. Two PET studies have found that its levels were increased in the ventral brainstem of individuals with schizophrenia, but found no differences compared to controls in the striatum or thalamus[76,77]. This is in contrast to the post-mortem studies discussed above[28], but in keeping with a study showing increased VMAT2 density within platelets from individuals with schizophrenia[78].

PET: presynaptic dopamine function

Multiple methods exist for quantifying aspects of presynaptic dopamine function.

Several studies have investigated dopamine release capacity by studying the reaction of the dopamine system to an acute challenge, be that pharmacological such as amphetamine, or psychological such as a reward or stress task[79]. Animal studies have shown that comparing ligand binding during the challenge to binding at baseline allows one to infer the amount of dopamine release induced by the task[80].

Alternatively, one can obtain a measure of baseline synaptic dopamine levels by comparing a baseline scan with a scan obtained following the administration of a dopamine depleting agent such as alpha-methylparatyrosine.

Finally, radiolabelled L-DOPA can be used to quantify dopamine synthesis capacity. Radiolabeled L-DOPA is taken up by dopamine neurons, where it is converted by aromatic L-amino acid decarboxylase to dopamine, which is then sequestered in vesicles within nerve terminals[81]. The rate of uptake provides an index of dopamine synthesis capacity.

Striatum

Studies have consistently demonstrated raised presynaptic dopamine function in schizophrenia, with Hedges' g=0.7 (Hedges' g is a measure of effect size, and values of 0.2 are typically considered small, those of 0.5 medium, and those of 0.8 large[82]). The studies using a challenge paradigm show larger effect sizes (g=1.0) compared to those quantifying dopamine synthesis capacity (g=0.5)[83]. The hyperdopaminergic state associated with schizophrenia appears greatest within the dorsal striatum[83].

Further evidence for pathophysiological relevance comes from studies showing a direct association between synthesis capacity and the severity of positive psychotic symptoms[84-86]. The relationship with other symptom domains is less clear: an inverse relationship with depressive symptoms[87] and a lower synthesis capacity associated with worse cognitive performance[88] have been reported.

Extra-striatal regions

Outside of the striatum, dopamine synthesis capacity can only be reliably measured in a limited number of brain regions, such as the substantia nigra and the amygdala, using current techniques[89]. Two studies have found increased dopamine synthesis capacity in the substantia nigra[90,91], although this was not observed in another[92]. One study also found raised dopamine turnover in the amygdala[91].

Although cortical dopamine receptors are predominantly D1-type, D1 receptor ligands are not reliably displaceable, and therefore not suitable for challenge or displacement studies. Cortical D2 receptors do exist, but studies are complicated by their sparsity[93]. Furthermore, although challenge paradigms have demonstrated validity in the striatum, the results of cortical studies are harder to interpret, with displacement not always observed[94].

One study using amphetamine challenge in combination with the high-affinity ligand FLB-457 found reduced dopamine release in the prefrontal cortex in individuals with schizophrenia[95]. Two other recent FLB-457 studies adopted psychological challenges. One of these used a psychological stressor, which did not induce cortical tracer displacement in either patients or controls[96]. The other used a cognitive test of executive function, which did show lower tracer displacement in patients, but interpretation was complicated by the fact that, again, the task did not consistently induce dopamine release[97]. A study using ^{18}F-fallypride found no differences between patients and controls in terms of stress-induced cortical dopamine release[98].

Two studies have examined dopamine release in the substantia nigra. One used a stress challenge and found an increased release in patients[99]; the other adopted an amphetamine challenge and found a non-significant reduction[95].

PET: dopamine across the psychosis spectrum

Several studies have investigated dopamine function in subjects at clinical high risk for psychosis. Initial studies showed evidence of raised presynaptic dopamine function in these individuals[100-102]. However, this was not seen in the largest study to date[103]. This may potentially result from the fact that raised presynaptic striatal dopamine function appears to be limited to those subjects who subsequently develop psychosis[104], and transition rates have declined in recent years.

A study of healthy individuals that experience auditory hallucinations also found no difference in striatal dopamine synthesis capacity compared to healthy controls without hallucinations[105]. Studies in individuals at increased genetic risk for schizophrenia, such as patients' relatives and individuals with 22q11.2 deletion syndrome, have also not shown consistent differences from controls in terms of presynaptic dopamine function[106-108].

Studies in psychotic individuals with diagnoses other than schizophrenia, such as bipolar disorder and temporal lobe epilepsy[86,109], have found raised striatal dopamine synthesis capacity. This finding, along with the inconsistent evidence in people at increased clinical or genetic risk, may suggest that increased striatal dopamine synthesis capacity is associated with psychosis across psychiatric diagnoses, rather than being an underlying risk factor for schizophrenia.

Studies of dopamine receptor densities in individuals at both clinical[99,100,110] and genetic[107,110-113] high risk are similar to those in individuals with schizophrenia, in that they have shown no clear differences from controls.

Summary of PET findings

The studies reviewed above provide consistent evidence of a striatal presynaptic hyperdopaminergic state in schizophrenia (see Table 2), and little consistent evidence of altered D2/3 receptor levels. It remains uncertain as to whether abnormalities exist with regard to other dopamine receptors, or with cortical dopamine function.

Consequences of dopaminergic dysfunction

Prediction errors, salience and positive symptoms

After its role in movement was established, preclinical findings suggested that dopamine also played a role in signalling reward[114]. Later work demonstrated that signalling more specifically related to the discrepancy between expected and received reward – a reward prediction error[115]. More recently, it has been demonstrated that firing is not exclusively tied to reward prediction, but rather can occur in response to a wide range of salient stimuli[116-120], and that in more dorsal regions of the striatum dopamine signalling is particularly associated with threat-related stimuli[118,119].

Several related theories have proposed how disruption to normal dopamine function could underlie positive psychotic symptoms such as delusions and hallucinations[121-123]. Dysregulated dopamine neuron firing will aberrantly signal that irrelevant stimuli are of importance, thereby imbuing percepts and thoughts with abnormal salience, in turn leading to inappropriate associations and causal attributions[124]. There are also mechanisms through which uncoordinated dopamine signalling may contribute not only to the generation of delusional beliefs, but also to the imperviously rigid form of delusional thought[123,125].

Recent work has attempted to identify more precisely the mechanisms through which dopaminergic dysfunction may contribute to symptoms. The experience of a stimulus depends not only on the sensory inputs resulting from that stimulus, but also on prior expectations regarding the probability of a percept. Auditory hallucinations appear to result from a stronger influence of prior expectations upon sensory percepts[126], and this increased weighting of priors has been associated with greater levels of amphetamine-induced dopamine release in the striatum[127].

In terms of understanding the development of delusions, a combined PET and MRI experiment found that dopamine release was related to neural signalling of belief updates rather than just sensory surprise[128]. This suggests that aberrant dopamine signalling may lead to irrelevant stimuli being understood as meaningful, the clinical relevance of which is supported by the finding that participants who displayed more aberrant belief updating showed greater subclinical paranoid ideation[128].

In addition to mesostriatal dopamine signalling, several cortical regions have also been implicated in salience processing[129,130]. The salience network comprises the anterior cingulate cortex and bilateral insula, and abnormalities of this network have been proposed as a core feature of schizophrenia pathophysiology[131]. The network has a key role in orchestrating dynamic switching between brain states, for example between a resting state and states associated with performing cognitively demanding tasks[132]. It is of relevance that dopamine signalling also plays a role in dynamic reorganization of brain states[133,134]. Recent work has demonstrated that mesostriatal dopamine signalling and salience network connectivity are tightly linked[135], although whether this relationship is disrupted in schizophrenia is not known.

Reward, motivation and negative symptoms

Reward and punishment are fundamental drivers of behaviour, and reinforcement learning models formalize the relationship between reward, states and behaviour. Prediction errors

allow the value of states and actions to be learnt, and are a key signal in many reinforcement learning models. Given the central role of dopamine in both coding prediction errors and in the cortical representation of environmental states, several studies have used this framework to explore the behavioural consequences of disrupted dopamine signalling[136].

Cortical D1 receptors play a central role in shaping the accurate neural representation of environmental states, by allowing precise inhibition of neural activity[137]. Reduced cortical dopamine signalling means that stimuli associated with reward cannot be accurately encoded, effectively foreclosing their ability to guide behaviour[137]. Furthermore, reduced cortical dopamine signalling may mean that reward-related representations are short-lived, with the consequence that, even if correctly represented, the motivational properties of reward-associated stimuli have a briefer impact[137].

Dopamine neurons fire in response to stimuli that have been previously associated with reward, and guide behaviour towards actions associated with previous reward[138]. A striatal hyperdopaminergic state may mean that reward-associated stimuli have reduced motivational influence, as aberrantly high background levels of dopamine signalling reduce the signal-to-noise ratio of adaptive phasic signalling[139]. This mechanism also has the potential to reduce the appetitive properties of a given reward, thereby reducing its impact to shape future behaviour, and accounting for negative symptoms such as anhedonia and amotivation[140-142]. This reduced signal-to-noise ratio may account for the reduced striatal activation to reward observed with fMRI in individuals with schizophrenia[51].

Cortical dopamine and cognitive symptoms

Cognitive symptoms of schizophrenia include deficits in working memory, executive function, and information processing. They occur prior to the onset of frank psychosis and account for a significant proportion of the morbidity associated with the illness[143-145].

The dorsolateral prefrontal cortex is central to many cognitive processes, and both functional and structural pathology of the region has been linked to the deficits seen in schizophrenia[146]. The molecular changes underlying cognitive symptoms, however, are unknown. Given the importance of D1 receptor signalling for cognition[147], reduced cortical dopamine signalling has long been hypothesized to contribute to the cognitive symptoms observed in schizophrenia. As discussed above, however, evidence regarding D1 receptors in schizophrenia is inconclusive, and there has been only a single study demonstrating reduced cortical dopamine release[95].

On the basis of preclinical work using a model of striatal D2 overexpression, it has also been proposed that excessive striatal dopamine signalling may lead to reductions in cortical dopamine and associated cognitive symptoms[7]. Therefore, it appears that both reduced and excessive dopamine signalling can have deleterious effects on cognition, which may contribute to the fact that there has been minimal success in developing dopamine modulating treatments for cognitive symptoms of schizophrenia[4,145].

GLUTAMATE

As reviewed above, there is significant evidence that dysfunction of the dopamine system is involved in the pathogenesis of schizophrenia. This may, however, occur downstream of other pathophysiological processes. Furthermore, schizophrenia is a heterogenous disorder, and dopaminergic dysfunction may not play a significant role in some individuals, while in others it may be only one of several pathological mechanisms.

Substantial evidence has accumulated implicating the glutamate system in the pathogenesis of schizophrenia. Glutamate is the major excitatory neurotransmitter in the central nervous system, and, in contrast to the anatomically localized cell bodies of dopamine neurons, glutamatergic neurons are widespread throughout the brain.

Glutamate receptors show considerable variety, and are classified as either ionotropic or metabotropic. Ionotropic receptors include the NMDA and the non-NMDA receptors – kainate and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA). NMDA and non-NMDA receptors are normally co-localized on neurons, and act synergistically in that the NMDA receptor has slower kinetics and tends to enhance depolarization initiated by non-NMDA receptors.

Following the discovery of the psychotomimetic effects of NMDA antagonists, the NMDA receptor has become a primary focus when considering potential glutamatergic dysfunction in schizophrenia. Below we examine the evidence associating schizophrenia with glutamatergic abnormalities, consider how these abnormalities may lead to symptoms, and review the potential of glutamate modulating agents as treatments.

Indirect evidence for glutamatergic dysfunction in schizophrenia

Animal models

The administration of NMDA antagonists to non-human primates and rodents has been shown to induce a variety of schizophrenia-like behaviours, such as sensorimotor gating impairments, increased locomotion, abnormal repetitive movements, and cognitive and social deficits[38]. NMDA antagonism has also been shown to lead to hippocampal hypermetabolism, similar to that which has been observed in schizophrenia[148,149].

A genetic animal model that reduced levels of the NMDA co-agonist D-serine was associated with neurobiological changes similar to those observed in schizophrenia, such as reduced dendritic spine density and hippocampal volume[39]. Several other genetic mice models, such as those involving inactivation of D-amino oxidase[40] and reduction of the synaptic protein dys-

bindin[41], also show NMDA receptor hypofunction accompanied by behavioural and neurobiological changes analogous to those observed in schizophrenia.

CSF and post-mortem studies

Initial small studies of CSF found reduced glutamate levels in patients, but these findings were not replicated[42,43]. However, CSF and post-mortem brain levels of kynurenic acid, an NMDA receptor antagonist, have consistently found to be raised, although not plasma levels[44].

Post-mortem studies investigating structural alterations of glutamate neurons have generally found reductions in dendrite arborization, spine density, and synaptophysin expression across frontal and temporal regions[45].

mRNA expression of specific glutamate receptors and their subunits has also been investigated across multiple brain regions. Although several studies have found reduced expression of NMDA receptor subunits such as GRIN1, GRIN2A and GRIN2C, these have not been consistently replicated across brain regions[45], although – when regions are examined individually – there is evidence of reduced GRIN1 expression in the hippocampus[45]. A recent study examining samples from over 500 individuals with schizophrenia found increased exon skipping in GRIN1, that would affect the extracellular ligand binding site[30]. Fewer studies have examined protein expression of these subunits, and these are also inconsistent in their findings[45].

There have also been a small number of studies investigating enzymes involved in glutamate metabolism. Excitatory amino acid transporters (EAAT) remove glutamate from the synaptic cleft. After reuptake from the synapse, glutamine synthetase converts glutamate to glutamine. When glutamine is delivered to neurons, it is converted back to glutamate by glutaminase. There is some preliminary evidence that both mRNA and protein levels of EAAT2, the transporter responsible for the majority of glutamate uptake, are reduced in frontal and temporal areas of patients with schizophrenia, while glutaminase mRNA levels and enzymatic activity have been found to be raised in two studies examining, respectively, the thalamus and dorsolateral prefrontal cortex[45].

Although the caveats regarding post-mortem studies discussed above remain, several of the findings covered here are consistent with impaired functioning of the NMDA receptor. In addition to the direct pathology suggested by the findings relating to GRIN1, the reduced expression of EAAT2 and the increased expression of glutaminase may be understood as compensatory responses attempting to increase synaptic glutamate levels.

Psychopharmacology of NMDA antagonists

The administration of NMDA receptor antagonists, such as phencyclidine and ketamine, to healthy controls has been repeatedly shown to induce manifestations similar to the positive, negative and cognitive symptoms of schizophrenia[46]. It has been demonstrated that NMDA receptor blockade by these compounds is both necessary and sufficient for their psychotomimetic effects[150].

These drugs have also been shown to exacerbate a similarly wide spectrum of symptoms in individuals with schizophrenia, in contrast to amphetamines, which predominantly worsen positive symptoms[151]. Furthermore, it has been shown that anti-NMDA receptor encephalitis may be associated with psychiatric presentations that resemble schizophrenia in some individuals[152]. NMDA antagonism has, therefore, been proposed to be a superior pharmacological model of schizophrenia, compared to amphetamines, given its ability to more reliably induce negative as well as positive symptoms[153,154].

Acute NMDA antagonist administration has typically been employed in experimental settings, since chronic administration to healthy controls cannot be ethically undertaken. However, chronic ketamine users show subthreshold psychotic symptoms across positive, negative and cognitive domains[47,48], and a subgroup of these chronic users develop a persisting psychosis that is more similar to schizophrenia than that induced by acute single dose ketamine administration[155].

Imaging glutamate in vivo

Proton magnetic resonance spectroscopy

Proton magnetic resonance spectroscopy (^{1}H-MRS) is the most frequently used technique for investigating the glutamate system in vivo. It does not require the use of ionizing radiation, and is significantly cheaper than PET.

^{1}H-MRS does, however, have several drawbacks, including the fact that it is unable to distinguish between intra- and extracellular compartments[156]. Glutamate does not act solely as a neurotransmitter, but is involved in protein synthesis and nitrogen metabolism, and is a precursor to GABA[157]. This means that it is not possible to infer whether differences between patients and controls relate to synaptic glutamate concentrations, as opposed to alterations in these other functions of glutamate. Even if one assumes that detectable abnormalities relate to differences in synaptic neurotransmission, it is not possible to determine whether this is secondary to differences in synaptic levels, as opposed to presynaptic dysfunction, or altered reuptake of glutamate.

At higher field strengths, glutamate and its metabolite glutamine can be distinguished, while at lower strengths the concentration of both, often abbreviated to Glx, is all that can be accurately quantified. Glutamine is synthesized from glutamate following the uptake of synaptic glutamate by astrocytes, and glutamine levels have been taken to be a marker of glutamate neurotransmission. However, as with glutamate, glutamine takes part in multiple cell process, which complicates interpretation[158].

There have been over fifty ^{1}H-MRS studies of the glutamate system in schizophrenia. A synthesis of their findings is complicated by methodological differences, notably in the imaging

sequences used, the brain regions studied, and the patient cohorts enrolled. Notwithstanding these issues, a meta-analysis of these studies has found several relatively consistent findings[159]. There is evidence that Glx (g=0.4) and glutamate (g=0.6) levels are raised in the basal ganglia, that glutamine concentration is increased in the thalamus (g=0.6), and that Glx levels are raised in the medial temporal lobe (g=0.3) in patients with schizophrenia (Table 2).

Although these effect sizes are in some instances comparable to those observed for presynaptic dopamine function, they represent considerably less studies. In the case of both glutamate in the basal ganglia and glutamine in the thalamus, only three studies have been performed, and as such these findings should be regarded as preliminary. The increased Glx levels observed in the medial temporal lobe represent 18 studies (13 in schizophrenia and 5 in clinical high-risk individuals).

If taken to reflect synaptic glutamate levels, the temporal lobe findings are consistent with the post-mortem findings discussed above, and the PET study discussed below, which suggest that receptor dysfunction is accompanied by compensatory changes that increase synaptic glutamate levels. This is also consistent with studies that have found hippocampal hyperactivity in psychosis, potentially resulting from dysfunction of NMDA receptors located on GABAergic interneurons[9,148,149].

In recent years, several studies have been performed using higher magnetic field strengths of up to 7 Tesla. Higher field strength has greater sensitivity, enabling greater separation of glutamate and glutamine peaks, and allowing for more accurate quantification. Two studies in first-episode patients have shown reduced glutamate concentrations in the anterior cingulate cortex[160,161], while another only found this in a subset of patients with predominantly negative symptoms[162]. No difference has been observed in several other investigations[163-166]. Overall this suggests that, even at high field strengths, group differences are inconsistent.

Another recent development is functional MRS. This involves acquiring multiple measures during a task or other stimulus, to investigate dynamic changes in metabolite measures. Changes in ^{1}H-MRS measures during a stimulus are proposed to result from compartmental shifts, as glutamate located extracellularly may contribute more to the signal. This results from the fact that, within presynaptic vesicles, metabolite movement is restricted, and therefore may have a faster T2 relaxation rate[167].

A study using a heat pain stress found a reduced anterior cingulate cortex glutamate response in individuals with schizophrenia compared to healthy controls[168], although interpretation is complicated by the fact that baseline glutamate levels were higher in patients. A similar pattern was seen in a study using a cognitive task in which patients showed reduced anterior cingulate glutamate response compared to controls[166].

Other neuroimaging techniques

Given the limitations of ^{1}H-MRS in determining the precise nature of glutamatergic abnormalities, several attempts have been made to develop radioligands capable of directly measuring glutamate receptors.

One study found reduced NMDA receptor binding in the left hippocampus of patients with schizophrenia, but no further studies have been attempted, in part due to concerns regarding a lack of specificity of the tracer. A recent study using a tracer for the metabotropic glutamate receptor 5 found no patient-control differences[169]. New tracers are under development, but lack of specificity remains an ongoing problem when attempting to image glutamate receptors[170].

^{13}C-MRS is another non-invasive imaging technique. It has lower sensitivity compared to ^{1}H-MRS, but, when combined with a ^{13}C labelled infusion, it has the potential to overcome some of the limitations associated with ^{1}H-MRS, specifically as regards to characterizing the glutamate-glutamine cycle[171]. This technique has been adopted to show that the majority of energy production in the brain supports glutamatergic activity and, although studies are yet to be performed in schizophrenia, it has recently been used in humans to show that ketamine increases glutamate-glutamine cycling[172,173].

Glutamate chemical exchange saturation transfer (GluCEST) is another novel technique for measuring glutamate in vivo. In addition to improved sensitivity, it allows for whole brain imaging without the need to specify a single voxel[174]. It has so far been used in a single investigation, which reported reduced glutamate levels in individuals with schizophrenia and those at clinical high risk, compared to healthy controls[175].

Glutamate across the psychosis spectrum

As with imaging of the dopamine system, efforts have been made to characterize glutamatergic function in individuals at clinical and genetic high risk for psychosis. Similarly, although a meta-analysis suggested that increased Glx levels might exist in the medial frontal cortex in individuals at clinical high risk of psychosis[165], recent studies have been negative[176-178], and there appear to be no clear differences between at-risk individuals and controls.

Given that ^{1}H-MRS measures of glutamate have been consistently shown to decline with age across the frontal cortex, anterior cingulate, hippocampus and basal ganglia[179-181], it may be that schizophrenia is associated with a distinct trajectory of change, and so differences only become detectable later in the time course of the illness.

Consequences of glutamatergic dysfunction

Unlike dopamine neurons, which are restricted to relatively well circumscribed anatomical pathways, glutamate signalling occurs ubiquitously throughout the brain and, as a result, dysfunction of this system has the potential to account for a wide range of impairments.

However, given the limitations regarding techniques for directly quantifying the glutamate system in vivo, there is a paucity of

direct evidence regarding the precise nature of glutamatergic dysfunction in schizophrenia, and studies looking at the relationship between ^{1}H-MRS measures of glutamate and symptom severity have produced inconsistent findings[182]. Indeed, both increased and decreased level of glutamate as measured by ^{1}H-MRS have been proposed to support a hypothesis of NMDA hypofunction in schizophrenia[183,184].

NMDA receptors, sparse coding and memory

NMDA receptors play a vital role in orchestrating several cognitive processes, including working memory[185]. One of the mechanisms involved in the efficient cortical representation of information is that of sparse coding.

Different cortical cell classes encode information differently. More superficial cell layers code "sparsely". This means that only a small proportion of cells within a region will be spiking, and information is thus encoded spatially[186]. This is in contrast to deeper layers, where the majority of cells may be firing, and information is encoded by variations in the rate of spiking[186]. Sparse coding involves great spatial precision in terms of the area of excitation, and this is mediated by strong lateral inhibition secondary to dense GABAergic interneuron networks within the superficial layers[187].

Sparse coding allows the maintenance of multiple mnemonic networks, and also the protection of encoded memories from distractors[137]. Disruption to sparse coding mechanisms has been shown to lead to the development of false memories in animal models[188]. Both individuals with schizophrenia and healthy controls administered NMDA antagonists display phenomena that may result from impaired sparse coding – a smaller working memory buffer, decreased mnemonic precision, and false alarms in working memory[137,189]. Decreased inhibition secondary to hypofunction of NMDA receptors on GABAergic interneurons could account for a disruption to the spatial precision of superficial layer firing, but this remains to be definitively tested.

Excitatory/inhibitory balance and neuronal oscillations

Synchronized neuronal oscillations are associated with a wide range of cognitive processes, such as working memory. These oscillations result from a tightly maintained balance between excitatory and inhibitory populations of neurons, and can be measured in vivo using electroencephalogram (EEG).

The balance between excitation and inhibition is crucial for normal physiological function, and NMDA receptors play a critical role here. Disruption to this balance has been proposed to result in the EEG abnormalities observed in schizophrenia. This disorder is associated with increased resting gamma oscillations, that have been linked to cognitive symptoms[190]. This disruption of normal oscillatory activity mirrors what has been observed with ketamine administration in healthy volunteers.

A range of molecular alterations have been proposed to potentially lead to excitatory/inhibitory imbalance in schizophrenia, including excessive pruning of dendritic spines, and intrinsic GABAergic abnormalities[191]. Another candidate mechanism is that of NMDA hypofunction. NMDA antagonists preferentially act on GABA interneurons, because these neurons have a more depolarized membrane potential. It has also been proposed that, in schizophrenia, NMDA hypofunction may preferentially affect interneurons[192], which would in turn lead to greater activity of pyramidal neurons. This uncoordinated increased activity may underlie disruptions to normal oscillatory activity mentioned above, and act as noise, impairing the ability of coordinated activity to be passed down to subcortical regions[150].

FACTORS UNDERLYING GLUTAMATERGIC AND DOPAMINERGIC DYSFUNCTION

Genetic factors

Over a hundred risk loci have been associated with schizophrenia by large scale genome-wide association studies (GWAS)[195]. Given the evidence implicating dopamine in the disorder, it is surprising that only one of the loci was found to be associated with the dopamine system, specifically the dopamine D2 receptor.

Analyses specifically looking at genes involved in dopamine synthesis, signalling and metabolism have also been unable to find a signal other than for D2 receptors, and this accounts for a negligible proportion of the overall genetic risk[196]. However, other loci strongly linked to schizophrenia, such as 10q24.32, have shown associations with dopamine synthesis capacity[197], as have polymorphisms of the gene DISC1[198]. Although relatively small sample sizes were used, these findings suggest that genetic factors related to schizophrenia may indirectly affect the dopamine system.

In the case of glutamate, many genes involved in the development and maintenance of glutamatergic synapses are not only implicated by loci significantly associated with schizophrenia in GWAS[193,195], but also by studies examining rarer genetic risk factors[199,200]. This includes genes that directly code for components of glutamate receptors, such as GRIN2A, GRIA1 and GRM3, and genes involved in facilitating glutamatergic neurotransmission through other means, such as that coding for serine racemase (SRR). These results provide some of the strongest support that disruption of glutamatergic signalling is a fundamental component of schizophrenia pathophysiology.

Induced pluripotent stem cells (iPSCs) allow for the generation of live neurons, in vitro, from somatic cells taken from patients. These neurons are best conceptualized as modelling fetal brain tissue, primarily reflecting an underlying genetic architecture, distilled from environmental exposures[201]. The use of iPSCs can be particularly valuable in elucidating the effects of genetics in a polygenic disorder such as schizophrenia, where disease risk is encoded by complex networks of genes, the functional consequences of which are not easily intuited.

Several studies using this technique have investigated how the dopamine system may be affected. One study found reduced DAT expression, indicating immaturity in dopaminergic neurons derived from individuals with schizophrenia[202]. Another study, however, found that dopamine neurons derived from patients

tended to develop more rapidly, and showed increased dopamine release[203]. Small sample sizes and differences in experimental protocols likely contributed to these discrepancies[204].

iPSCs have also been used to study the glutamate system in neurons derived from individuals with schizophrenia. Two studies have demonstrated deficits in glutamate receptor signalling in patient-derived cells[205,206], and a follow-up study identified specific gene modules associated with these deficits in glutamatergic signalling[201]. One investigation found reduced glutamate release in schizophrenia-derived cells differentiated to hippocampal dentate gyrus cells[207], while another found delayed maturation of both dopaminergic and glutamatergic neurons, and that glutamatergic neurons displayed a reduced ability to form synaptic contacts[202].

Environmental factors

Acute psychosocial stress has been shown to induce striatal dopamine release[208,209]. Measures of presynaptic dopamine function are raised in migrants, and those that have experienced childhood trauma, both of which are risk factors associated with schizophrenia[210-213]. However, another risk factor for schizophrenia, heavy cannabis use, is associated with blunted dopamine synthesis capacity and release[214,215].

Although acute stress has been shown to increase cortical glutamate level in preclinical models, this has not been demonstrated in humans using ^{1}H-MRS[216,217]. ^{1}H-MRS studies in cannabis users generally report reduced glutamate levels in both cortical and subcortical areas, which is in keeping with animal work[218]. Of note, a recent iPSC study showed that, in neurons derived from individuals with schizophrenia, tetrahydrocannabinol administration led to depressed glutamate signalling[219].

Neural circuits and dopamine-glutamate interactions

The evidence discussed above suggests that, while the dopamine hypothesis can account for the positive symptoms of psychosis, it is less clear whether it can fully account for negative and cognitive symptoms. Similarly, while glutamatergic models of psychosis are able to replicate a wide range of symptoms of psychosis, they do not directly account for the finding of increased presynaptic striatal dopamine function, nor the clinical effectiveness of dopamine antagonists. This suggests that dysfunction in both systems contributes to the pathophysiology of schizophrenia, and highlights the need to understand how these two systems may interact.

Much research has investigated dopamine-glutamate relationships in humans using pharmacological challenges. Amphetamine administration has been shown to increase cortical glutamate levels, as measured using ^{1}H-MRS[220], but dopamine antagonists do not have consistent effects on glutamate levels as measured using ^{1}H-MRS[221]. Several, but not all, PET studies have found that ketamine administration is associated with striatal dopamine release[222]. While glutamatergic dysfunction may encourage dopaminergic disinhibition, it is clear that this is not the only route to symptoms, given that dopamine antagonists do not entirely ameliorate the effects of NMDA antagonists[223].

Recent studies have combined PET and MRI measurements in the same individuals to investigate this relationship without the use of pharmacological modulation. One study in healthy individuals found that increased dopamine synthesis capacity in the ventral striatum was associated with both reduced cortical and increased striatal levels of glutamate[224]. This is in keeping with the imaging studies discussed above, in which both increased dopamine and glutamate measures were observed in the striatum in schizophrenia, which could potentially result from increased activity of glutamatergic projection to the striatum. Other studies found the same relationship between cortical glutamate and striatal dopamine in clinical high-risk and first-episode psychosis patients, but not in controls[225,226].

Theories linking glutamate and dopamine have proposed that defective NMDA receptors on cortical GABA interneurons result in inadequate inhibition of glutamatergic projections to the midbrain. This, in turn, may overstimulate mesostriatal dopamine neurons. In order to account for purported cortical dopamine deficits, it has also been proposed that overactive glutamatergic projections might overstimulate GABA interneurons in the ventral tegmental area, and thereby overinhibit mesocortical projection neurons[227].

The first of these proposed mechanisms has support from studies demonstrating ketamine-induced release of striatal dopamine. It is also in line with the ^{1}H-MRS studies discussed above, if the increased basal ganglia glutamate levels observed in schizophrenia are taken to represent increased activity of cortical projections. The second mechanism remains speculative[222].

It is likely, however, that the relationship between glutamate and dopamine is not one-way but bidirectional. As mentioned above, human studies have suggested that modulation of the dopamine system affects cortical glutamate levels. Preclinical studies have shown that mice genetically modified to have upregulated dopaminergic signalling display disrupted glutamatergic signalling of thalamocortical neurons[228]. Furthermore, cortical dopamine receptors have been shown to influence local glutamate release[229].

The wide range of pathways potentially linking the two systems, and the potential for opposing effects depending on the number of interneurons within a circuit, means that it is not possible to disentangle precise mechanisms with currently available neuroimaging methods.

TREATMENT

Dopamine modulating treatments

Antipsychotics are effective treatments for positive symptoms in the majority of patients with a diagnosis of schizophrenia. However, about one third of patients show persistent positive symptoms despite treatment, and this has been termed treatment-resistant schizophrenia[230].

Recent studies have suggested that dopamine synthesis capacity may predict which patients respond to treatment. An initial study found that dopamine synthesis capacity was only raised in those with a treatment-responsive illness[84], which is consistent with a more recent prospective study[231].

Even when effective in treating positive symptoms, dopamine antagonists do not typically show significant benefit for negative and cognitive symptoms. This is expected if these symptoms do not primarily relate to the hyperdopaminergic state, and particularly so if they result from deficits in dopaminergic signalling.

All currently licensed antipsychotics exert their dopaminergic effects primarily at postsynaptic D2 receptors, which is downstream of the presynaptic hyperdopaminergic state that has been observed in molecular imaging studies. There are currently a number of treatments in development which attempt to correct dysregulated dopamine function further upstream.

Apomorphine was shown to be an efficacious treatment in an early clinical trial[232]. Although later studies did not consistently replicate this finding[4], a recent investigation suggested that this drug may normalize dopaminergic activity, potentially via agonism of presynaptic autoreceptors[233]. Another upstream approach involves agonism of trace amine type 1 receptors. This has been shown preclinically to both reduce midbrain dopamine neuron activity, and reduce the locomotor response to amphetamine[234].

Finally, the PET studies discussed above have demonstrated that presynaptic dopaminergic dysfunction is greatest in the dorsal striatum[83], and muscarinic receptor 4 positive allosteric modulators specifically inhibit dorsal striatal dopamine release, with efficacy demonstrated in some clinical trials[235,236].

The dopamine system may also be more indirectly regulated via upstream circuits. The potential of glutamate signalling to modulate dopamine neurotransmission has been discussed above. Reduced functioning of GABAergic interneurons has also been suggested to contribute to disinhibition of dopamine neurons, and alpha 5 selective GABA agonists have been proposed as means of addressing this. Although neuroimaging and preclinical work provides conceptual support, efficacy in patients is yet to be demonstrated[4].

There is also the chance of intervening downstream of postsynaptic receptors. Stimulation of D2 receptors inhibits cyclic adenosine monophosphate (cAMP) production, while phosphodiesterase inhibitors have an opposing effect by preventing cAMP breakdown. Phosphodiesterase inhibitors may therefore have the potential to block the downstream effects of excessive D2 signalling, and also the potential benefit of boosting cortical D1 signalling[237]. Although clinical trials testing these compounds have not yet been successful[4], there is a significant variability in the regional expression of phosphodiesterase inhibitor subtypes, and those showing the greatest cortical expression remain to be tested[238].

Glutamate modulating treatments

Glutamate modulating treatments for schizophrenia fall into two camps: those that aim to augment NMDA signalling, and those that aim to reduce levels of synaptic glutamate proposed to be pathologically raised as a result of NMDA hypofunction. A general challenge for the development of glutamatergic treatments is that they will typically have relatively global effects, whereas pathology may be confined to discrete cell types such as NMDA receptors on specific GABAergic interneurons[239,240].

Since directly augmenting synaptic glutamate levels could have pathologically excitotoxic effects, efforts at augmenting NMDA signalling have focused on the receptor's glycine modulatory site. For activation of the NMDA receptor, glycine or D-serine has to bind to the glycine modulatory site on GluN1 subunit, in addition to glutamate binding at the GluN2 subunit. Agonists of the glycine modulatory site – including glycine, D-serine and D-cycloserine – have demonstrated the ability to attenuate the psychotogenic effects of NMDA antagonists in preclinical studies, although this has not been clearly demonstrated in humans [150].

A meta-analysis of clinical trials in individuals with schizophrenia suggested that D-serine may be effective in the treatment of negative symptoms[241], but a relatively large trial was subsequently negative[242]. The same meta-analysis also suggested that glycine may have a benefit for overall symptoms as well, but large scale trials are needed for clear confirmation of this effect[241]. A meta-analysis of glutamate positive modulators in the treatment of cognitive symptoms, including D-serine and glycine, did not demonstrate benefit over placebo[243].

Poor blood-brain barrier penetration by glycine and some of the other co-agonists means that occupancy of the glycine modulatory site may be insufficient to exert clinically measurable effects. To address this, an alternative approach has involved attempts to increase synaptic glycine levels by blocking the glycine type 1 transporter, thereby inhibiting removal of glycine from the synapse.

Bitopertin, a glycine type I transporter inhibitor, appeared to be a promising compound in this regard, showing good blood-brain barrier penetration, with encouraging results in early clinical trials[244]. However, later trials were not successful, perhaps due to the unusually high placebo responses, or the use of chronic patient populations, given that there is some evidence that intervention is likely to be more effective in early illness stages[245]. More recently, another glycine type I transporter inhibitor was shown to increase long-term potentiation (a marker of neuroplasticity) in individuals with schizophrenia, and the compound awaits testing in clinical trials[246].

Another potential approach may be to lower levels of kynurenic acid, which is an endogenous antagonist of the glycine modulatory site[247]. Cyclooxygenase-2 inhibitors reduce kynurenic acid levels, and celecoxib has shown benefit as an adjunctive treatment in early psychosis, but not chronic illness[248]. However, a recent in vitro study found that celecoxib did not significantly reduce kynurenic acid levels, while parecoxib and niflumic acid did[249]. So, it may be that other cyclooxygenase-2 inhibitors have the potential for greater efficacy.

Based on findings that NMDA antagonism increases synaptic glutamate levels, the second general approach has focused on

hypotheses that NMDA hypofunction may result in pathologically raised levels of glutamate, and therefore inhibiting the release of glutamate from terminals may be therapeutic[150,250].

The metabotropic glutamate 2 receptor (mGluR2) is located presynaptically on glutamate neurons, where it acts as an autoreceptor to regulate glutamate release[251]. Positive allosteric modulators of mGluR2 have been found to be effective in reducing the cognitive impairments induced by ketamine[252]. However, efficacy in clinical trials has not been consistently shown[253]. One complication in these trials was the high rate of placebo response.

Riluzole (2-amino-6-trifluormethoxy benzothiazole) has also been shown to reduce synaptic glutamate levels through a wide range of mechanisms, and an initial trial found it to be effective in treating negative symptoms in schizophrenia, potentially by altering striatocortical connectivity[254,255]. Similarly, lamotrigine inhibits glutamate release via inhibition of several ion channels, and attenuates the psychotomimetic effects of ketamine[256]. Lamotrigine has also shown efficacy as an adjunctive medication for clozapine-resistant schizophrenia, although studies to date are small and findings inconsistent[257].

Neuroimaging studies have suggested that treatment-resistant schizophrenia may not show the dopaminergic dysfunction seen in treatment-responsive schizophrenia[84,231,258], and that glutamatergic abnormalities may be of greater pathophysiological relevance in those cases of schizophrenia which do not respond to antipsychotic medications[259,260]. Supporting this view, there is evidence that cortical glutamate levels are higher in patients with treatment-resistant schizophrenia relative to responsive patients[261]. One of the reasons for unsuccessful clinical trials may therefore be that glutamate modulating treatments are only of significant benefit in a subgroup of patients.

OUTSTANDING QUESTIONS AND FUTURE DIRECTIONS

There are a number of outstanding issues when it comes to understanding the role of dopamine and glutamate in schizophrenia. In the case of glutamate, it is not possible to separate extra- and intracellular compartments using MRS, and we cannot accurately probe receptors and synaptic glutamate levels in vivo. As a result, it is not currently possible to precisely characterize the nature of glutamate dysfunction in schizophrenia. It remains unclear whether synaptic glutamate levels are abnormal, whether receptors are altered, and where any alterations might be localized within the brain.

Because of this, it is not clear whether treatments should aim to reduce synaptic glutamate levels or augment glutamatergic neurotransmission[150]. This likely contributes to the fact that to date no glutamate modulating agents exist that demonstrate unequivocal efficacy in schizophrenia.

There is a need for radioligands with reliable binding at the NMDA receptor to allow for investigation of receptor abnormalities in schizophrenia. PET ligands for other proteins involved in glutamatergic signalling, such as AMPA receptors, enzymes involved in glutamate synthesis and metabolism, and the kynurenine pathway, would also represent a considerable advance. In the meantime, other methods, such as functional MRS, ^{11}C-MRS, GluCEST and 7T ^{1}H-MRS, may advance our understanding by allowing more precise inferences regarding the nature of glutamatergic abnormalities in schizophrenia.

Imaging studies have provided more information when it comes to the dopamine system. However, several questions remain unanswered, such as the nature of cortical dopamine function in schizophrenia, whether a cortical hypodopaminergic state co-exists with the striatal hyperdopaminergic condition, and how dopaminergic dysfunction evolves across illness course.

The improved resolution of PET cameras has allowed for greater anatomical precision in identifying the locus of dopaminergic dysfunction in schizophrenia. Early hypotheses had suggested that this dysfunction might be characterized by aberrant mesolimbic function. However, the use of new PET cameras has demonstrated that the greatest patient-control differences are in the dorsal striatum[83]. The resolution of PET is still relatively coarse, however, and this limits the precision with which inferences can be made about which specific neuron groups are affected.

In addition to advances in hardware, further progress may be made by employing novel methods, such as super-resolution techniques, in which multiple low-resolution images are combined to create a high-resolution image, or deep learning methods, where anatomical information from an MRI scan is used to help improve the resolution of the PET image[262,263]. The limited resolution of in vivo imaging techniques means that it is difficult to directly test circuit level hypotheses regarding the nature of disrupted glutamate-dopamine interactions in schizophrenia. Instead, hypotheses regarding circuit interactions are largely based on preclinical, post-mortem and pharmacological studies, but await direct testing in patients.

Translation of research findings to clinically useful applications is not straightforward, and compounds acting though mechanisms other than dopamine receptor antagonism have not consistently shown efficacy in clinical trials. However, there exists a range of novel mechanisms for manipulation of both glutamate and dopamine signalling that show potential and await clinical testing. As discussed above, it may be that certain treatments are only of benefit in specific subgroups of patients, and clinical benefit may therefore be optimized by stratifying participants on the basis of underlying neurobiology[231,259]. Given the coarseness of current clinical measures[264], the development of imaging biomarkers to evaluate treatment effects at a neurobiological level may assist in moving the field forward[265].

The non-linearity inherent to neural signalling within a complex network means that, even if one disregards potential inconsistencies between studies, a coherent integration of existing findings is challenging. The combination of large datasets across illness phases, biophysical networks models to link molecular pathology to the macroscale dysfunction observed with neuroimaging, and carefully designed experiments to test and finesse

these models is one route to integrating what at times appears to be a disparate collection of findings[266,267].

CONCLUSIONS

The hypothesis that dopamine signalling is altered in schizophrenia is supported by animal studies, post-mortem research, and the clinical effects of drugs that either block or accentuate dopaminergic neurotransmission. In addition, over the past 25 years, substantial evidence has accumulated from PET studies that there is increased dopamine synthesis and release capacity in schizophrenia, that is greatest within the dorsal striatum.

Genetic findings do not provide strong support for the idea that dopaminergic dysregulation is a primary abnormality. Rather, it appears that the dopaminergic dysfunction is more likely to develop downstream of abnormalities in other systems, including the glutamatergic system. It also appears that environmental factors may play a significant role in the development of dopaminergic dysregulation. Dopamine antagonists remain the mainstay for pharmacological treatment of schizophrenia, but there is increasing evidence that these are not effective for all patients.

Evidence for glutamate playing a role in the pathophysiology of schizophrenia initially came from the psychotomimetic effects of NMDA antagonists. While preclinical and post-mortem findings are consistent with this hypothesis, there is limited support from imaging studies. However, in contrast to dopamine, recent genetic findings do provide support for the view that glutamatergic abnormalities may play a major role in schizophrenia pathophysiology. However, progress is hampered by the challenges involved in precisely characterizing the system in vivo, and, while a wide range of glutamate modulating agents have been investigated, none have clear clinical efficacy.

Despite the limitations described, as regards both treatment efficacy and direct evidence for dysfunction, the dopamine and glutamate hypotheses of schizophrenia remain influential and relevant. This is not least because, as recent data demonstrate, they possess the flexibility to accommodate new findings, and to provide ongoing potential avenues for the development of novel treatments.

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