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Glutamate and dopamine in schizophrenia: an update for the 21st century

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Abstract

The glutamate and dopamine hypotheses are leading theories of the pathoaetiology of schizophrenia. Both were initially based on indirect evidence from pharmacological studies supported by post-mortem findings, but have since been substantially advanced by new lines of evidence from *in vivo* imaging studies. This review provides an up- date on the latest findings on dopamine and glutamate abnormalities in schizophrenia, focusing on the *in vivo* neuroimaging studies in patients and clinical high risk groups, and considers their implications for understanding the biology and treatment of schizophrenia. These findings have refined both the dopamine and glutamate hypotheses, enabling greater anatomical and functional specificity, and have been complemented by preclinical evidence showing how the risk factors for schizophrenia impact on the dopamine and glutamate systems. The implications of this new evidence for understanding the development and treatment of schizophrenia are considered, and the gaps in current knowledge highlighted. Finally the evidence for an integrated model of the interactions between the glutamate and dopamine systems is reviewed, and future directions discussed.

Keywords

schizophrenia; psychosis; mechanisms; treatment; antipsychotic; imaging; etiology; PET; MR; dopamine; glutamate; NMDA; D2

Introduction

Schizophrenia is a common, severe mental illness (Jablensky *et al.*, 1992; Jablensky, 2000), and a leading cause of adult disease burden (Whiteford *et al.*, 2013). It has a lifetime prevalence of about 0.7%, with a peak age of onset in the early twenties in men, and three or four years later in women (Saha *et al.*, 2005). The disorder is characterised by psychotic

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symptoms such as delusions and hallucinations, negative symptoms such as social withdrawal and amotivation, and cognitive impairments. In addition to the high morbidity and mortality rate associated with schizophrenia, the health and social care costs for the illness are substantial: total costs of care for individuals with schizophrenia in the UK amount to 16.7 billion EURO per annum, while for Europe the figure is 93.9 billion EURO (Gustavsson *et al.*, 2011). Antipsychotic drugs are the mainstay of treatment for schizophrenia, but are inadequate in a substantial proportion of patients (Andrews, 2003). Better understanding of the neurobiology underlying the disorder is needed to improve the use of existing drugs and inform the development of new drugs.

Two of the most influential hypotheses concerning the neurobiology underlying the disorder involve dopamine and glutamate. Both hypotheses were proposed several decades ago, but new evidence, particularly from *in vivo* imaging studies and preclinical findings on the role of these neurotransmitters has refined understanding of the nature of dopamine and glutamate dysfunction in schizophrenia. The purpose of this review is to provide an overview of both hypotheses and an up-date on the recent findings relevant to them, focussing on the *in vivo* neuroimaging findings. Finally it considers the degree to which they may be integrated, the implications of the new findings for treatment, and the limitations of current evidence.

Dopamine

Dopamine: early evidence for its involvement in schizophrenia

The dopamine hypothesis of schizophrenia initially arose from several indirect sources of evidence. A key source was studies showing that administration of amphetamine and other compounds which increase extracellular concentrations of dopamine can induce psychotic symptoms similar to those seen in schizophrenia (see review (Lieberman *et al.*, 1987)). This was supported by studies of drugs, such as reserpine and alpha-methyl-*para*-tyrosine that deplete dopamine levels (Carlsson *et al.*, 1957), which showed that these drugs reduced psychotic symptoms (Campden-Main and Wegielski, 1955; Arnold and Freeman, 1956; Carlsson *et al.*, 1973; Walinder and Skott, 1976).

Further evidence for dopamine's involvement in schizophrenia came in the 1970s, with observations that the clinical effectiveness of antipsychotic drugs was directly related to their affinity for dopamine receptors (Seeman and Lee, 1975; Seeman *et al.*, 1976; Creese *et al.*, 1976). As a result of this discovery, the leading hypothesis at this time was that schizophrenia arises as a result of abnormalities in dopamine receptor density (Matthysse, 1973; Snyder, 1976).

Whilst these findings implicated dopamine in schizophrenia, this was in a rather general way and there were a number of limitations on the interpretation of the evidence. For example, both amphetamine and reserpine affect other brain monoamines as well as dopamine (see review (Davis *et al.*, 1991)). Furthermore, at this time there was no clear indication of the locus of dopaminergic abnormality in the living brain.

Post-mortem studies are able to provide anatomical detail and biochemical specificity. Early post-mortem studies suggested that the neuropathological changes in schizophrenia included both an increase in striatal dopamine levels, and an increase in D2 receptor density (Owen *et al.*, 1978; Mackay *et al.*, 1982), but no change in dopamine transporter (DAT) densities (Pearce and Seeman, 1990).

More recent studies have provided greater detail regarding the nature of these pre and post-synpatic dopamine changes. For example, recent research has shown tyrosine hydroxylase, the rate-limiting enzyme involved in the synthesis of dopamine, is significantly increased in the substantia nigra of patients with schizophrenia compared to patients with depression and healthy controls (Howes *et al.*, 2013a), indicating that there is increased capacity for production of dopamine in the midbrain origin of dopamine neurons as well as their striatal terminals. Other recent work has refined understanding of the nature of the D2 receptor changes. A study including 176 post mortem samples from patients with schizophrenia showed the expression of the presynaptic D2 autoreceptor was increased, while the expression of predominantly postsynaptic variants were decreased in the dorsolateral prefrontal cortex compared with controls (Kaalund *et al.*, 2013). The hypothesis that D2 receptors are somehow altered in schizophrenia is supported by genetics' findings that have shown a clear association between the DRD2 gene and schizophrenia. (Ripke *et al.*, 2014).

The potential relevance of the D4 receptor was initially highlighted by post mortem work showing a sixfold increase in D4 receptor density in schizophrenia (Seeman *et al.*, 1993). This finding appeared to bear particular relevance given clozapine's unique clinical properties and its high level of binding to the D4 receptor not shared by other antipsychotics. Subsequent attempts at replication, however, were mixed (Reynolds and Mason, 1994; Murray *et al.*, 1995).

Dopamine receptors form dimers with themselves and with other receptors in *in vitro* models. A number of studies have recently looked at the role that dimerisation of the dopamine receptor may play in schizophrenia. In a study of 15 schizophrenia patients Wang and colleagues found a 278% increase in expression of D2 dimers compared to controls, while D2 monomers were decreased to 69% of the control level (Wang *et al.*, 2010). In addition there is preliminary evidence concerning D2 heteromers from a post-mortem study that found that D1-D2 heteromers were increased in schizophrenia in the globus pallidus, although the study included only 4 patients with schizophrenia (Perreault *et al.*, 2010). This is complemented by earlier post-mortem findings that showed the inhibitory link between D1 and D2 receptors is reduced in patients with schizophrenia (Seeman *et al.*, 1989). These findings highlight the potential impact of changes in dimerization, although, as it is not yet possible to directly measure dimerization *in vivo*, these finding await testing *in vivo* in patients.

In summary, post-mortem studies continue to identify abnormalities in both the presynaptic and post-synaptic dopaminergic system in schizophrenia. However, one potential limitation of post mortem studies is the difficulty in controlling for the confounding effects of antipsychotic medication, and it is plausible that the presynaptic and post-synaptic changes observed are predominantly iatrogenic. Another difficulty is linking the changes to the

expression of symptoms and the development of the disorder, often many years before the patient died. In order to address these issues evidence from living patients is required. The following sections consider the latest *in vivo* neurochemical imaging evidence in patients.

Dopamine and schizophrenia: *in vivo* imaging evidence

Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) imaging allows the *in vivo* quantification of many aspects of dopaminergic function in the brain, including dopamine synthesis, the degree of dopamine release in response to stimuli, and the availability of the post-synaptic dopaminergic receptors and transporters (Kim *et al.*, 2013a). Over the last two decades or so, advances in PET/SPECT technology and their application has enabled the major aspects of the dopaminergic hypothesis of schizophrenia to be tested and refined (McGuire *et al.*, 2008). Studies initially focussed on dopamine D2 receptors and the action of antipsychotic drugs, before examining other aspects of the dopaminergic system

Antipsychotic drugs and dopamine D2 receptors—All currently licensed antipsychotic drugs block D2 dopamine receptors. However, they also act at other receptors in the brain, including other dopamine receptor subtypes and those for serotonin, histamine, norepinephrine and acetylcholine (Stahl, 2013). It was initially far from clear which receptor mediated the clinical response to antipsychotic treatment. Molecular imaging studies with both SPECT (e.g.: (Brücke *et al.*, 1991; Brücke *et al.*, 1992; Pilowsky *et al.*, 1993; Volk *et al.*, 1994; Klemm *et al.*, 1996)) and PET (e.g.: (Farde *et al.*, 1988; Baron *et al.*, 1989; Wolkin, 1989; Nordström *et al.*, 1992; Nordstrom *et al.*, 1993; Goyer *et al.*, 1996; Kapur *et al.*, 1996)) have extended the *in vitro* studies on dopamine receptors and antipsychotics from the 1970s in several crucial ways. First, they have demonstrated that all antipsychotic drugs cross the blood-brain-barrier. Second, they have shown that they block D2/3 striatal receptors *in vivo* at clinically effective doses. These data extended the *in vitro* findings to patients, and have provided the foundation for studies in which the relationship between D2 occupancy and clinical response could be established.

The relationship between D2 occupancy, clinical response, and side effects is not linear (see review Howes *et al.* 2009a)). Little response is seen when occupancy is below 50%, response increases from this point but the risk of extrapyramidal side effects increases when occupancy reaches around 75% (Nordstrom *et al.*, 1993). These findings have been replicated in a double blind study of first-episode patients. This study found a threshold D2 occupancy of 65% was found to best separate responders from non-responders: at 65% receptor occupancy, 80% of responders were above the threshold whilst 67% of the non–responders lay below the 65% threshold (Kapur *et al.*, 2000). Given the central role of dopamine receptors in the mode of action of antipsychotics, it is not surprising that considerable focus has been directed at determining if there are alterations in D2 receptors *in vivo*.

Dopamine D2 Receptor availability in schizophrenia—The action of dopamine on post-synaptic receptors constitutes the final stage in transmitting the dopaminergic neuronal impulse to post-synaptic neurons. As all clinically available antipsychotics block D2

receptors, over the last three decades many studies have investigated whether D2 receptor availability is altered in schizophrenia compared to control subjects.

It is important to note that the radioligands used to image dopamine receptors in vivo such as [11C]raclopride (Malmberg *et al.*, 1993) and [123I](S)-(-)-3-iodo-2-hydroxy-6-methoxy-N-[(1-ethyl-2-pyrrolidinyl)methyl]benzamide ([123I]IBZM) (Videbaek *et al.*, 2000) show significant D3 receptor binding in addition to their D2 binding. Thus it is theoretically possible that an elevation in one could be obscured by a reduction in another. [11C]-(+)-4-propyl-9-hydroxynaphthoxazine ([11C]-PHNO) is an agonist radiotracer that shows higher affinity for D3 receptors than D2. Studies in schizophrenia using this tracer have not shown any difference in binding from controls (Graff-Guerrero *et al.*, 2009). This suggests that alterations in D3 receptor availability are not masking changes in D2 receptors, although the development of selective D2 tracers would be useful to definitively establish this.

There have been at least twenty-two published studies, but, after an initial positive finding, subsequent results have been inconsistent. The most recent meta-analysis (Howes *et al.*, 2012b) found increased D2/3 receptor density in patients with schizophrenia, but the effect size was small (d=0.26, p=0.049). However the picture is complicated by large heterogeneity between studies. In the subgroup analysis of studies that exclusively considered antipsychotic-naïve patients no significant differences from controls was found, whereas significant differences were found in the studies that included patients who had received antipsychotic treatment. Other sources of heterogeneity include different radiotracers used and differences in duration of illness. In addition, elevated baseline dopamine levels in schizophrenic patients could potentially mask differences in receptor density. Nevertheless the most likely implications are that there is not a major elevation in D2 receptor availability in drug naïve patients and that antipsychotic treatment leads to D2 receptor upregulation in some patients. The potential effect of antipsychotics on D2 receptors has been tested directly in a PET imaging study comparing D2 binding potentials between a group of treatment naïve patients with a group that had been treated with antipsychotics long term that underwent temporary antipsychotic withdrawal (Silvestri *et al.*, 2000). Significantly increased D2 receptor availability was found in the group that had experienced long term antipsychotic treatment, consistent with the idea that there is D2 upregulation with antipsychotic treatment.

Changes in D1 receptor densities have been less thoroughly investigated and are complicated by variation in the populations studied and the radiotracers employed. Two studies looking at chronic, medicated patients have shown widespread cortical and striatal reductions in D1 receptor densities (Hirvonen *et al.*, 2006; Kosaka *et al.*, 2010). One study of antipsychotic naïve patients and one of naïve and previously treated patients showed increased densities of D1 receptors in the prefrontal cortex in patients (Abi-Dargham *et al.*, 2002; Abi-Dargham *et al.*, 2012). Conversely another study of antipsychotic naïve and medication free patients showed a decrease in prefrontal cortex densities (Okubo *et al.*, 1997), while a further study of purely naïve patients showed no significant differences (Karlsson *et al.*, 2002). Interpretation of the studies is further complicated by the discovery that the radiotracers used (NNC 112 and SCH 23390) also bind to the 5HT2A receptor (Ekelund *et al.*, 2007; Catafau *et al.*, 2010),. This serotonergic receptor has been implicated in the aetiology of

schizophrenia, and its involvement has been further supported by a recent meta-analysis of post-mortem findings (Selvaraj *et al.*, 2014). Further studies using more specific radiotracers are thus needed to determine the nature of D1 changes in schizophrenia.

Fewer studies have investigated D2/3 receptor density in extrastriatal brain regions. A recent meta-analysis did not find any significant differences for receptor densities in the thalamus, temporal cortex or substantia nigra; while in other brain regions where it was not possible to conduct a meta-analysis findings were either statistically insignificant or have not been replicated (Kambeitz *et al.*, 2014).

Finally, the D2 receptor may exist in two intraconvertible (high and low) affinity states for agonist binding and it has been proposed that the balance between these two states is altered in schizophrenia (Seeman *et al.*, 2006). An initial study with *[11C]-(+)-PHNO ([11C]-(+)-4-propyl-9-hydroxynaphthoxazine), a* radiotracer selective for the high affinity state as well as D3 receptors, suggested that no alteration is apparent in the absence of dopamine depletion (Graff-Guerrero *et al.*, 2009). However further work has suggested that the radiotracer used may be unable to distinguish between the two receptor states (Seeman, 2012), indicating that this issue remains unresolved.

Dopamine transporter levels—The dopamine active transporter (DAT) regulates dopaminergic transmission by removing dopamine from the synaptic cleft. The DAT is solely present in dopamine synthesising axons (Ciliax and Heilman, 1995), and because of this specificity in location it is a useful measure of the integrity of dopaminergic neurons. Early neurodegenerative theories of schizophrenia proposed that a change in the density of striatal dopamine terminals was fundamental to the disorder; one strand of this hypothesis was that hyperdopaminergic activity could itself be neurotoxic and lead to loss of dopaminergic neurons in the striatum (Lieberman *et al.*, 1990). Imaging of the DAT has allowed this hypothesis to be tested.

There have been thirteen PET or SPECT imaging studies that have addressed DAT density in schizophrenia. There is a large degree of heterogeneity between the studies with a number of inconsistent findings. Recent meta-analyses (Howes *et al.*, 2012b; Chen *et al.*, 2013) found no evidence for a difference in striatal DAT receptor densities in patients with schizophrenia, and this finding has been replicated in a subsequent study of almost fifty antipsychotic-naïve patients (Chen *et al.*, 2013). This essentially negative result suggests that the dopaminergic abnormalities observed in schizophrenia are not secondary to abnormalities in the DAT, nor due to differences in the density of pre-synaptic dopaminergic neurons.

Dopamine synthesis and release—In dopamine neurons radiolabelled L-DOPA is converted to dopamine and trapped in dopaminergic nerve terminals. The extent of radiolabelled L-DOPA uptake measured using PET thus provides an index of presynaptic dopamine synthesis capacity and the availability of dopamine for release from presynaptic terminals (see review by (Kumakura and Cumming, 2009)), and shows good test retest reliability in dopaminergic regions (Egerton *et al.*, 2010a). Meta-analysis of the studies using this technique shows a large elevation in dopamine synthesis capacity in schizophrenia compared with matched controls, with an effect size of 0.8 (Howes *et al.*, 2012b). With the

addition of three studies published after this meta-analysis, there have now been fourteen PET studies of dopamine synthesis capacity in patients with schizophrenia, summarised in table 1 (adapted from (Howes *et al.*, 2012b)).

Dopaminergic neurotransmission requires the release of dopamine from presynaptic terminals. This can be indexed *in vivo* using molecular imaging with radiotracers which bind to dopamine D2 receptors, such as [11C]raclopride or [123I]IBZM, as these radiotracers compete with dopamine to bind to dopamine D2 receptors. Decreased radiotracer binding following a pharmacological challenge that releases dopamine thus reflects increased extracellular dopamine (Egerton *et al.*, 2010b). All six investigations that have used this approach in schizophrenia have found evidence of significantly increased dopamine release in patients compared to control subjects (Laruelle *et al.*, 1999; Abi-Dargham *et al.*, 2009; Pogarell *et al.*, 2012) (see table 2). The extent of radiotracer displacement was approximately doubled in schizophrenic patients, and the degree of displacement correlated with the degree of worsening of psychotic symptoms. These findings have been recently been extended by using a social stress task in the place of the pharmacological challenge, and showing increased dopamine release to stress in schizophrenia (Mizrahi *et al.*, 2012).

An alternative method to index synaptic dopamine levels involves the use of alpha-methyl-p-tyrosine, a tyrosine hydroxylase inhibitor. This depletes intrasynaptic dopamine and therefore allows the level of baseline synaptic occupancy to be estimated from the subsequent increase in radiotracer binding. Two studies using this technique have shown increased baseline occupancy of D2 receptors in schizophrenia, indicating that extracellular dopamine concentrations are also increased at baseline in schizophrenia (Kegeles *et al.*, 2010) (see table 2).

Presynaptic dopamine dysfunction: state or trait marker?—Together, these studies provide compelling evidence that presynaptic dopamine availability and dopamine release are increased in schizophrenia. This raises the question is increased presynaptic dopamine a state marker of psychosis or a trait marker related to risk of schizophrenia?

In the studies where patients were acutely psychotic at the time of investigation, elevated dopamine synthesis capacity has been consistently detected (Hietala *et al.*, 1995; Hietala *et al.*, 1999; Howes *et al.*, 2009b), whereas elevated dopamine synthesis capacity has been less consistently detected in studies of chronic patients, with some studies not finding significant differences from controls (Dao-Castellana *et al.*, 1997; Elkashef *et al.*, 2000; Shotbolt *et al.*, 2011) whilst others have detected significant elevations (Reith *et al.*, 1994; Meyer-Lindenberg *et al.*, 2002; Mcgowan *et al.*, 2004; Howes *et al.*, 2013a). Similarly patients experiencing an acute relapse show evidence of significantly greater dopamine release than controls, and although patients in remission show greater dopamine release than controls in absolute terms, this was not statistically significant (Laruelle *et al.*, 1999).

In recent years a significant body of work has developed examining the prodromal phase of schizophrenia (see table 3). Howes *et al.* initially showed that dopamine synthesis capacity is increased in individuals with prodromal symptoms of schizophrenia (Howes *et al.*, 2009b), now replicated in an independent cohort (Egerton *et al.*, 2013), while later work showed that

the increase in capacity was specific to individuals that went on to develop a psychotic illness (Howes *et al.*, 2011b). Finally, the studies in the prodrome to schizophrenia provide evidence that dopamine synthesis capacity increases further with the onset of acute psychosis (Howes *et al.*, 2011a).

Taken together these findings suggest there is at least a component of presynaptic dysfunction that changes and is related to the acute psychotic state. However, this does not exclude the possibility that a further component is related to risk.

In order to determine whether increased synthesis capacity is a marker for risk of schizophrenia two studies have examined individuals with an increased genetic risk of schizophrenia. In a study of seventeen first degree relatives of individuals with schizophrenia Huttenen *et al.* (Huttunen *et al.*, 2008) found significantly increased dopamine synthesis capacity compared to controls. However, Shotbolt *et al.* did not find altered dopamine synthesis capacity in twins discordant for schizophrenia (Shotbolt *et al.*, 2011). As the twins in this study were predominantly dizygotic it remains possible that they had not inherited the genetic risk, and further studies are needed to determine if genetic risk is associated with dopamine dysregulation per se.

A contrasting approach has been to see whether increased synthesis capacity is present in individuals who experience psychotic-like symptoms but do not have a diagnosis of schizophrenia. Early research showed that psychotic symptoms secondary to temporal lobe epilepsy were associated with increased striatal dopamine synthesis capacity to a similar degree to that seen in schizophrenia (Reith *et al.*, 1994). This has also been shown to be the case in individuals with schizotypal personality disorder (Abi-Dargham *et al.*, 2004), while this has not found in healthy individuals who experience persistent sub-clinical auditory hallucinations but have never developed schizophrenia or functional impairment (Howes *et al.*, 2013b), suggesting presynaptic dopamine dysfunction is linked to clinical disorder rather than being a marker of psychotic-like experiences per se.

In summary, evidence from a number of studies indicates that presynaptic dopamine dysfunction has at least a state component, but the evidence that it is a trait marker is less clear cut. Research using healthy twin pairs has found evidence that environmental factors explain a substantial proportion of variation in normal presynaptic dopamine function (Stokes *et al.*, 2013). This fits with recent models that stress and other risk factors for psychosis impact on a vulnerable dopamine system to dysregulate it and lead to psychosis (Howes and Murray, 2014).

Linking dopamine to symptoms and environmental risk factors

The evidence reviewed above indicates there is a presynaptic hyperdopaminergic abnormality in schizophrenia and that antipsychotics act by blocking D2 receptors to treat psychotic symptoms. In and of themselves however, these findings do not explain how a biochemical abnormality can account for the phenomenology of the psychotic experience. The aberrant salience model (Kapur, 2003; Heinz and Schlagenhauf, 2010; Winton-Brown *et al.*, 2014)seeks to provide this link.

Animal studies provide support for dopamine's role as a mediator in assigning motivational salience to internal or external stimuli, and thereby determining which stimuli grab attention and drive behaviour (Bromberg-Martin *et al.*, 2010). It is proposed that in schizophrenia, the elevation in presynaptic dopamine leads to its release in the absence of appropriate stimuli (Winton-Brown *et al.*, 2014). Dysregulated release is thought to lead to the attribution of salience to irrelevant stimuli simply by virtue of the stimuli's temporal association with the dopaminergic signalling. This aberrant attribution of salience is thought to account for psychotic phenomena such as ideas of reference, and patients' accounts of the prodromal phase of psychosis, where everyday occurrences are imbued with a sense of inexplicable significance (Fusar-Poli *et al.*, 2008). There is certainly evidence that untreated and drug naïve patients with schizophrenia show alterations in processing motivationally salient stimuli (Juckel *et al.*, 2006; Schlagenhauf *et al.*, 2009; Nielsen *et al.*, 2012). In addition there is also evidence that patients with current delusions and people with prodromal-type symptoms who are at risk of psychosis show greater assignment of importance to irrelevant stimuli, supporting the aberrant salience hypothesis (Roiser *et al.*, 2009; Roiser *et al.*, 2013). This hypothesis has been integrated with cognitive models (Garety *et al.*, 2001) to explain the paranoid flavour of many delusional experiences by proposing that social adversity leads to the development of paranoid biases, which adds a persecutory colour to the misattribution of salience (Howes and Murray, 2014). The subsequent crystallisation of this experience into a delusion can be viewed as an individual's attempt to construct a coherent narrative that accounts for their experiences, and influenced by their personal and cultural background.

The combination of this aberrant salience model with the dopaminergic abnormalities described above, and evidence on the impact of environmental and neurodevelopmental risk factors has contributed to the dopamine hypothesis being revised (Howes and Kapur, 2009; Howes and Murray, 2014). However this is predominantly a model of psychosis in schizophrenia.

Cognitive and negative symptoms of schizophrenia are responsible for a major proportion of the disability associated with the disorder (Ho *et al.*, 1998; Rosenheck *et al.*, 2006). An influential reconceptualization of the dopamine hypothesis in the 1990s proposed that sub-cortical hyperdopaminergia was secondary to cortical hypodopaminergia, in particular in frontal regions (Davis *et al.*, 1991). The association between frontal dysfunction and cognitive impairment seen in schizophrenia is well established (Barch and Ceaser, 2012). Furthermore research in patients with chronic schizophrenia has shown that cortical dysfunction is linked to increased striatal dopamine dysfunction (Bertolino *et al.*, 2000; Meyer-Lindenberg *et al.*, 2002), in line with this hypothesis. However, as these studies were in chronic patients, it was not clear whether this reflected the long-term sequelae of the condition or was linked to the development of the disorder. More recent research in individuals showing prodromal indicators of schizophrenia has found that increased striatal dopamine synthesis capacity is associated with worse performance on cognitive tasks (Howes *et al.*, 2009b), and that it is correlated with altered cortical function during cognitive tasks prior to the onset of schizophrenia as well (Fusar-poli *et al.*, 2010; Allen *et al.*, 2012a; Allen *et al.*, 2012b). This indicates that a common factor could underlie both processes, but does not indicate which is primary, or what the common factor is. Whilst it remains plausible that the common factor is cortical dysfunction, animal models using mice that

selectively overexpress striatal D2 receptors suggest that increased dopaminergic activity in the striatum may be able to account for both deficits in incentive motivation (Ward *et al.*, 2012) and in cognitive functioning (Simpson *et al.*, 2010), indicating that striatal dopaminergic dysfunction could contribute to the negative symptoms and cognitive impairments. These findings thus suggest that sub-cortical dopamine dysfunction could contribute to the cognitive and negative symptoms of schizophrenia as well as psychosis.

Limitations of the dopamine evidence in schizophrenia

The findings reviewed above provide evidence that there is a dopaminergic abnormality underlying schizophrenia, localise it to presynaptic dopamine dysfunction and link this to the symptoms of the disorder. However there are a number of findings that remain inadequately accounted for. These are discussed below.

Treatment resistance and non-dopaminergic forms of schizophrenia—One third of individuals with schizophrenia do not respond to non-clozapine antipsychotics (Mortimer *et al.*, 2010) despite high levels of D2 occupancy (Kapur *et al.*, 2000). Furthermore they do not respond to manipulations that deplete presynaptic dopamine either (Remington *et al.*, 2012). The implication is that for a significant number of patients the pathophysiological basis of their symptoms involves more than dopaminergic excess, or may be unrelated to dopaminergic dysfunction. Demjaha *et al.* have shown that dopamine synthesis capacity appears was raised in individuals with a treatment responsive illness but not in treatment resistant patients (Demjaha *et al.*, 2012). This is in agreement with earlier findings that found increased synaptic dopamine was predictive of treatment response (Abi-dargham *et al.*, 2000). Overall this suggests that there may be a ‘non-dopaminergic’ sub-type of schizophrenia (Howes and Kapur, 2014).

Negative and cognitive symptoms—Whilst dopaminergic dysfunction has been linked to negative and cognitive symptoms, and there are plausible mechanisms to explain this (as reviewed above), the direction of causality has yet to be established (Howes *et al.*, 2012a). Furthermore, the challenge studies provide evidence that dopamine elevation, albeit to supra-physiological levels, reduces negative symptoms (Laruelle *et al.*, 1999), which is not consistent with a simple model of presynaptic dopamine dysregulation underlying negative symptoms. This could be accounted for by the hypothesis that there are regionally selective changes, with low cortical dopamine accounting for negative and cognitive symptoms (Laruelle, 2014). However, this hypothesis remains to be tested with *in vivo* imaging studies, although this is now possible (Narendran *et al.*, 2009; Narendran *et al.*, 2014). Notwithstanding this, in clinical practice the effects of dopamine antagonists and partial agonists on cognitive impairments and negative symptoms are modest at best (Murphy *et al.*, 2006), and may even worsen cognitive function(Kim *et al.*, 2013b). This implies that either the dopamine modulating tools currently employed are blunt instruments or that other pathways, such as those involving glutamate, contribute to cognitive dysfunction.

Dual diagnosis—Substance dependence is common in people with schizophrenia (Buckley *et al.*, 2009) and a number of studies have examined this population. Decreased amphetamine induced dopamine release has been demonstrated in dual diagnosis patients

compared to healthy controls (Thompson *et al.*, 2013). Similarly, in clinically high risk individuals those that were cannabis dependent showed reduced dopamine release (Mizrahi *et al.*, 2013). Imaging of dopamine synthesis capacity in individuals who experience psychotic symptoms when they smoke cannabis showed significantly reduced striatal [^{18}F]-DOPA uptake compared to healthy volunteers (Bloomfield *et al.*, 2014). These findings indicate that the link between substance abuse and psychosis may involve a pathway that is distinct from the striatal presynaptic dopamine dysfunction described above.

Glutamate

The NMDA receptor hypofunction hypothesis

Excitatory neurotransmission in the brain is primarily glutamatergic, with glutamatergic neurons utilising between 60 and 80 percent of total brain metabolic activity (Rothman *et al.*, 2003). Glutamatergic neurotransmission occurs through metabotropic and ionotropic glutamate receptors, which are each subdivided into 3 groups. Group I metabotropic glutamate receptors (mGluR1 and mGluR5) are mainly postsynaptic, whereas group II (mGluR2 and mGluR3) and III (mGluR4, mGluR6, mGluR7 and mGluR8) are primarily presynaptic and modulate neurotransmitter release (Kew and Kemp, 2005). Ionotropic glutamate receptors are named after the agonists originally found to selectively activate them: a-amino-3-hydroxy-5-methyl-4-isoazolepropionic acid (AMPA), kainate and N-methyl- D-aspartate (NMDA) (Dingledine *et al.*, 1999; Kew and Kemp, 2005).

The involvement of glutamatergic mechanisms in schizophrenia has been hypothesised for many years. There are reports as far back as 1949 of patients with schizophrenia being treated with glutamic acid (Kintzinger and Arnold, 1949). One of the earliest reports of glutamatergic abnormalities in living patients was the finding of reduced CSF glutamate levels in patients with schizophrenia (Kim *et al.*, 1980). Despite early optimism, other groups failed to replicate this finding (Perry, 1982; Korpi *et al.*, 1987). However, since that time, there has a growing body of evidence for alterations in other aspects of glutamatergic neurotransmission in schizophrenia. The glutamate hypothesis of schizophrenia originally formulated that there was a simple deficit in glutamatergic neurotransmission in the condition. This theory has been modified and developed over the years and, although many glutamate receptors have been implicated, the prevailing hypothesis is for the primary involvement of NMDA receptor dysfunction (Stone *et al.*, 2007).

Indirect evidence for glutamate's involvement

Post mortem and genetic studies—Post mortem studies provide evidence for alterations to glutamatergic functioning in schizophrenia. Studies of NMDA receptor expression in post mortem samples have produced some positive findings such as reduced NMDAR1 subunit density in the superior frontal cortex (Sokolov, 1998) and the superior temporal cortex (Humphries *et al.*, 1996). However, overall findings regarding NMDA receptor density have been inconsistent (McCullumsmith *et al.,* 2012). It seems that the abnormality in schizophrenia may primarily be aberrant glutamate receptor localisation as opposed to a generalised deficit (Hammond *et al.,* 2014). This abnormality could arise as a result of changes in glutamate receptor trafficking molecules (Funk *et al.,* 2009).

Furthermore there is evidence for a variety of functional changes affecting the intracellular effects of the NMDA receptor that would have a major impact on glutamatergic signalling(Pitcher *et al.,* 2011; Funk *et al.*, 2012).

The potential role of glutamate in the pathophysiology of schizophrenia is also supported by recent genetics' findings (Ripke *et al.*, 2014). GRIN2A which codes for an NMDA receptor subunit was found to be associated with schizophrenia, as was SRR which plays a key role in pathways leading to the activation of the NMDA receptor.

NMDA receptor antagonists—The NMDA receptor dysfunction hypothesis of schizophrenia arose initially from the observation that non-competitive NMDA receptor antagonists, including phencyclidine (PCP), dizocilpine (MK-801) and ketamine, lead to immediate psychological effects, which closely resemble symptoms that occur in schizophrenia, including both positive and negative symptom domains (Krystal *et al.*, 1994; Morgan and Curran, 2006; Javitt, 2007). Psychotic-like symptoms are also seen in chronic ketamine users (Morgan *et al.*, 2009; Stone *et al.*, 2014). These findings led to the use of NMDA receptor antagonists as a model system for schizophrenia. Olney and Farber pursued this approach in animal models, and put forward the first NMDA receptor dysfunction hypothesis of schizophrenia. They showed that animals given NMDA receptor antagonists developed neurotoxic changes in cortical brain regions, which they suggested were similar to reductions in brain volume seen in patients with schizophrenia (Olney and Farber, 1995). They found that AMPA antagonists (among other compounds) could block the downstream effects of NMDA receptor antagonism on neurotoxicity, and hypothesized that glutamate release might underlie the neurotoxic effects. This was subsequently confirmed in microdialysis studies (Moghaddam *et al.*, 1997) and more recently with proton magnetic resonance spectroscopy (1H-MRS) studies following systemic ketamine administration in animals (Kim *et al.*, 2011).

Further research demonstrated that injection of the NMDA receptor antagonist MK-801 directly into cortical regions did not lead to any evidence of neurodegenerative changes, whereas injection into anterior thalamus led to the same cortical changes as seen with systemic administration (Sharp *et al.*, 2001), suggesting that the thalamus may be a critical site for NMDA receptor blockade in the generation of downstream effects by NMDA receptor antagonists, and, by extension, may also be a site of NMDA receptor dysfunction in schizophrenia (Olney and Farber, 1995; Stone *et al.*, 2007).

The method of administration of NMDA antagonists may have relevance regarding which aspect of the schizophrenia syndrome one is attempting to model. Acute administration of NMDA antagonists can perhaps be viewed as a model of acute psychosis. In contrast, longer-term administration shows potential as a model for chronic schizophrenia. Sub chronic administration of PCP to rats has been shown to cause long lasting deficits in set shifting ability (Egerton *et al.*, 2008), and reductions in functional connectivity (Dawson *et al.*, 2014) similar to those observed in chronic schizophrenia. While longer term administration of ketamine to rats produced cognitive deficits similar to those observed in chronic schizophrenia (Featherstone *et al.*, 2012). Furthermore, administration of NMDA

antagonists early in life results in long-term behavioural and neuroanatomical effects (Harris *et al.*, 2003) – providing a potential method for examining neurodevelopmental hypotheses.

The complete mechanism by which NMDA receptor antagonists lead to downstream increases in glutamate and neurotoxic changes in animals has not been fully elucidated, but evidence indicates it involves GABAergic interneurons. Specifically NMDA receptor antagonists have been shown to reduce GABAergic interneuron function (Homayoun and Moghaddam, 2007), and it is thought that this leads to an increase in pyramidal cell firing due to disinhibition (Olney and Farber, 1995). How NMDAR antagonism leads to reductions in GABAergic interneuron activity is less clear. It has been suggested that they may have preferential effects on NMDA receptors expressed on GABA neurons (Homayoun and Moghaddam, 2007), but this hypothesis has been contested (Rotaru *et al.*, 2012). An alternative hypothesis is that NMDA receptor antagonist-induced changes in reactive oxygen species levels may be a central component of this mechanism since reducing superoxide levels prevented ketamine-induced changes in interneuron activity (Behrens *et al.*, 2007). Furthermore, inhibiting reactive oxygen species formation blocks the behavioural effect of NMDA receptor antagonists in animals (Levkovitz *et al.*, 2007; Zhang *et al.*, 2007; Sorce *et al.*, 2010; Monte *et al.*, 2013).

Glutamatergic drugs treatments for schizophrenia—Findings from small clinical trials of glutamatergic drugs give further support to the NMDA receptor hypofunction hypothesis of schizophrenia (Stone, 2011). A number of studies have investigated NMDA receptor modulation, either via direct agonism at the glycine$_B$ modulatory site (using glycine or D-serine), or by increasing synaptic glycine levels through inhibition of glycine transporters (eg: sarcosine). A meta-analysis of published studies in 2009 reported that these drugs led to a significant improvement in residual positive and negative symptoms in patients with schizophrenia when administered in addition to existing antipsychotic treatment (Tsai and Lin, 2010). However, a subsequent, large clinical trial of D-serine, failed to show any benefit (Weiser *et al.*, 2012).

Bitopertin, a glycine transporter inhibiter developed by Roche, showed promising efficacy for negative symptoms in an initial trial (Umbricht *et al.*, 2014), and showed similar efficacy to olanzapine when used as monotherapy, in terms of patient readiness for discharge at 4 weeks compared to placebo (Bugarski-Kirola *et al.*, 2014). However, two recent Phase III studies, showed no benefit of bitopertin for negative symptoms (Goff, 2014). Thus, whilst the results of an ongoing study of bitopertin for reducing positive symptoms in patients with schizophrenia are awaited, the results to date suggest the effect size is modest at most. Overall there is some evidence that modulation of the glycine$_B$ site may be therapeutic in schizophrenia but this this has not been fully established.

Minocycline, a tetracycline antibiotic, has more recently raised interest in light of its neuroprotective properties. An initial open label study (Miyaoka and Yasukawa, 2008) showed large improvements in both positive and negative symptoms. More rigorous controlled studies (Levkovitz *et al.*, 2010; Chaudhry *et al.*, 2012; Liu *et al.*, 2014) examining its effect on negative symptoms have also shown clinically significant benefits. There are a number of potential mechanisms of action for minocycline, some of which involve the

glutamatergic system. In animal models minocycline has been shown to counter the effects of multiple NMDA antagonists (Levkovitz *et al.*, 2007; Zhang *et al.*, 2007; Fujita *et al.*, 2008). This effect on the glutamatergic system may be indirect and one possibility is that minocycline may modulate NMDA receptor signalling by inhibiting the formation of reactive oxygen species (Monte *et al.*, 2013).

The striking results recently observed in patients with schizophrenia following a single dose of sodium nitroprusside (Hallak *et al.*, 2013), may also have a glutamatergic mechanism underlying the clinical response. Preclinical work has shown that sodium nitroprusside is able to abolish the behavioural effects of phencyclidine (Bobanovic et al., 2000). The exact mechanism responsible for its clinical effects is not yet determined although there is some evidence that it may modulate NMDA receptor activity(Manzoni *et al.*, 1992).

Another line of evidence comes from studies of drugs targeting downstream glutamate release, such as lamotrigine, LY2140023 and topirimate. Lamotrigine, a drug which reduces glutamate release, has been reported to inhibit ketamine-induced psychosis-like effects in healthy volunteers (Hosák and Libiger, 2002), and related changes in brain function measured using fMRI (Deakin *et al.*, 2008). Early clinical data suggesting a benefit in partial responders to clozapine treatment (Dursun *et al.*, 1999) has received subsequent support in a meta-analysis, although effects were relatively modest (Tiihonen *et al.*, 2009).

LY2140023 is a drug developed by Eli Lilly as an agonist for presynaptic mGlu2/3 receptors to reduce glutamate release. It was found in an initial study to lead to significant improvements in positive and negative symptoms in patients with chronic schizophrenia (Patil *et al.*, 2007). However, a subsequent phase II trial did not show any significant benefit over placebo, possibly due to a particularly high level of placebo response (Kinon *et al.*, 2010).

Lastly, topiramate is a drug that may alter the downstream effect of excess glutamate through AMPA receptor antagonism. An initial positive open trial (Dursun and Deakin, 2001) using topirimate as an augmentation agent in treatment resistant schizophrenia was later replicated in a randomised controlled trial (Tiihonen *et al.*, 2005). It has also been shown to reduce the behavioural effects of MK-801 in rats (Deutsch *et al.*, 2002). However, as AMPA antagonism only occurs at higher doses, these inhibitory effects may occur through its enhancement of GABA transmission (Gibbs *et al.*, 2000), potentially calling into question a direct glutamatergic mechanism for the drug.

Overall, whilst there is clearly some evidence that glutamatergic drugs are effective treatments for schizophrenia, findings are somewhat mixed and where supported by meta-analysis the effect size is modest. These studies thus provide some evidence to support the involvement of glutamatergic dysfunction in schizophrenia, but there is nothing like the weight of evidence for treatment effects that there is for dopamine receptor blockers.

Glutamate – *In vivo* imaging studies

Neuroimaging studies of glutamatergic function in psychosis began later than the studies on the dopamine system. Nevertheless there is a substantial body of evidence from studies of

the effects of ketamine on brain function in healthy volunteers, and studies of brain glutamate levels in patients with prodromal and first episode psychosis, and with schizophrenia. These studies are summarised below, focusing on first episode and high risk studies as these ameliorate the risk of confounding by treatment effects (Poels *et al.*, 2014).

SPECT Studies—There is only one published SPECT study of NMDA receptor binding in patients with schizophrenia to date (Pilowsky *et al.*, 2006). This showed evidence of a relative deficit in NMDA receptor activity in the left hippocampus in unmedicated patients with schizophrenia (Pilowsky *et al.*, 2006). The study is relatively small, and no other groups have attempted to replicate the findings, possibly because of concern around levels of non-specific binding associated with the tracer used (N-(1-napthyl)-N'-(3-[(123)I]-iodophenyl)-N-methylguanidine (123I-CNS 1261)), a problem that affects all NMDA receptor tracers currently available (Knol *et al.*, 2009). Nevertheless it provides *in vivo* support for the NMDA hypofunction hypothesis, although this clearly requires further confirmation.

Proton Magnetic Resonance Spectroscopy Studies—Proton Magnetic Resonance Spectroscopy (1H-MRS) has been used to measure glutamate and glutamine levels in individuals at high risk of psychosis, as well as patients with first episode psychosis and chronic schizophrenia (Poels *et al.*, 2014). Glutamine has been suggested to be a marker of glutamatergic neurotransmission, as it is generated after synaptic glutamate is taken up into astrocytes(Bak *et al.*, 2006). 1H-MRS studies in schizophreniform psychosis and schizophrenia to date have generally found that individuals with clinical or familial risk, and those with first episode psychosis have increased glutamine in anterior cingulate cortex (Bartha *et al.*, 1997; Théberge *et al.*, 2002; Tibbo *et al.*, 2004; Stone *et al.*, 2009; Marsman *et al.*, 2013; Tandon *et al.*, 2013). The 1H-MRS studies of at risk or first episode populations are summarised in tables 4 and 5. In contrast, studies of patients with chronic schizophrenia have generally found normal or reduced cortical glutamate and glutamine levels (Block *et al.*, 2000; Kegeles *et al.*, 2000b; Théberge *et al.*, 2003; Ohrmann *et al.*, 2005; Ongur *et al.*, 2009; Rowland *et al.*, 2009; Tayoshi *et al.*, 2009; Lutkenhoff *et al.*, 2010; Natsubori *et al.*, 2013). However, a recent large, well designed study found, that patients with chronic schizophrenia had elevated glutamine:glutamate ratio (Gln/Glu) in anterior cingulate cortex, with a correlation between frontal Gln/Glu and positive psychotic symptoms (Bustillo *et al.*, 2014). Furthermore, in contrast to the data from a recently published meta-analysis (Marsman *et al.*, 2013), Gln/Glu increased with the age of patients rather than decreased (Bustillo *et al.*, 2014). The reason for this discrepancy is not clear, but may be due to differences in acquisition methodology, with this study employing a slightly longer echo time (40ms) for 1H-MRS acquisition (Bustillo *et al.*, 2014).

Another brain region with growing evidence for glutamatergic abnormalities in schizophrenia is the caudate nucleus. Glutamate and glutamine levels have been reported to be increased in individuals at familial risk for schizophrenia (Tandon *et al.*, 2013), and individuals at clinical risk and unmedicated patients with first episode psychosis have been reported to have increased glutamate in this brain region (de la Fuente-Sandoval *et al.*, 2011), although it appears to be affected by treatment, with four weeks of antipsychotic

medication leading to a normalisation of caudate glutamate levels (de la Fuente-Sandoval *et al.*, 2013).

There has been considerable interest in the possible utility of 1H-MRS in predicting treatment response in schizophrenia – with the theory that poor responders to conventional dopaminergic antipsychotic treatments may have more of a glutamatergic basis to their illness (Stone *et al.*, 2010). There have now been a number of studies that give preliminary support to this hypothesis. We recently found that patients with first episode psychosis who were poor responders to antipsychotic drugs had increased levels of glutamate scaled to creatine (Glu/Cr) in anterior cingulate cortex compared to those patients who had responded (Egerton *et al.*, 2012). Similarly we found that patients with established treatment resistant schizophrenia had increased anterior cingulate glutamate levels compared to controls and good responders (Demjaha *et al.*, 2014).

One problem with these studies is that the data were acquired cross-sectionally, and so it is not possible to determine whether the elevated glutamate measures in anterior cingulate were associated with treatment resistance, or were simply a surrogate marker of increased psychopathology at the time of scanning. For example, it has been shown that panic induced by cholecystokinin tetrapeptide leads to an acute increase in measured glutamate in anterior cingulate (Zwanzger *et al.*, 2013), and it is conceivable that a similar mechanism may occur in patients with symptoms of schizophrenia. However, a recent longitudinal study demonstrated that baseline Glx/Cr (reflecting the combination of GABA, glutamate and glutamine scaled to creatine) levels in the anterior cingulate of unmedicated patients predicted subsequent response to antipsychotic medication, with immediate responders having lower Glx/Cr (Szulc *et al.*, 2013). Thus, although mental state may modulate glutamate levels in anterior cingulate, this measure may, nonetheless, be a useful marker in predicting antipsychotic response. Longitudinal studies in first episode patients are required to clarify this point.

Limitations of the glutamate evidence in schizophrenia

Although several lines of evidence point to there being glutamatergic abnormalities in schizophrenia, there are a number of potential limitations to the theory. The use of 1H-MRS as the primary tool for the in vivo imaging of the glutamatergic system has some limitations. In particular 1H-MRS may not be able to distinguish between intra and extracellular compartments – so changes could reflect alterations in either compartment. The development of specific radiotracers for imaging of NMDA and AMPA receptors(Miyake *et al.*, 2011; Majo *et al.*, 2013; McGinnity *et al.*, 2014) will potentially enable the extracellular release of glutamate to be studied. 13C MRS is another potentially useful tool for allowing clearer understanding of the glutamatergic system(Mason *et al.*, 2007). A further limitation of the glutamate hypothesis is that it is not clear exactly what NMDA hypofunction means at the molecular level. This partly reflects the limitations of the evidence available at the moment.

Another major shortcoming at present is that there are no glutamatergic drugs currently on the market for schizophrenia, and trials of glutamatergic treatments have not shown a conclusive or strong effect in most cases. Secondly, due to the close interactions between

glutamate and dopamine, and the fact that ketamine has been reported to have effects on dopamine release, and may directly interact with high affinity D2 receptors(Kapur and Seeman, 2002; Egerton *et al.*, 2012), it may not be possible to interpret some of the ketamine findings as purely glutamatergic. Thirdly, it is clear that schizophrenia is unlikely to arise from a single cause in all cases (Horvath and Mirnics, 2014; Howes and Kapur, 2014), and thus glutamate abnormalities may be present only in a subset of patients with the illness, and possibly only at a particular phase of illness in these individuals(Marsman *et al.*, 2013). Finally, there is as yet no clear model to account for how the glutamate abnormalities observed could underlie the phenomenology of psychosis as seen in patients.

Integrating the dopamine and glutamate hypotheses

Whilst the evidence for the involvement of presynaptic dopamine dysfunction in the majority of cases of schizophrenia is compelling, dopamine dysfunction is most clearly linked to psychotic symptoms and the evidence for dopamine's involvement in the negative and cognitive symptoms is much less clear-cut (Javitt and Zukin, 1991; Tamminga *et al.*, 1995). In this respect glutamate models involving NMDA receptor blockade appear to be better able account for the range and nature of these aspects of schizophrenia (Javitt, 2010). A combination of both NMDA hypofunction and presynaptic dopamine dysfunction may therefore provide the best explanation of all the clinical aspects of schizophrenia.

The possibility that mesolimbic dopaminergic hyperactivity is secondary to diminished inhibitory control had been suggested before the glutamatergic system was explicitly identified as a candidate (Weinberger, 1987). Dopamine neurons are regulated by glutamatergic projections to the midbrain dopamine nuclei, which makes them potentially sensitive to changes in glutamatergic function (Miller and Abercrombie, 1996). This suggests that the dopamine function seen in schizophrenia could be secondary to altered glutamatergic function (McGuire *et al.*, 2008) (Figure 1.). Supporting this, preclinical studies show that NMDA blockers such as ketamine and PCP change dopamine neuron firing patterns, and increase dopamine release to a challenge such as amphetamine (Miller and Abercrombie, 1996; Tsukada, 2000; Balla *et al.*, 2003; Jackson *et al.*, 2004). There is also *in vivo* imaging evidence that ketamine administration leads to increased dopamine release in humans, as indexed by change in D2/D3 receptor PET tracer binding (Breier *et al.*, 1998; Smith *et al.*, 1998; Vollenweider *et al.*, 2000). Moreover baseline D2/D3 receptor availability is associated with increased sensitivity to the psychotogenic effects of ketamine in humans (Vernaleken *et al.*, 2013), further supporting the close interaction between these two systems. However, other groups have found evidence for elevated dopamine release following ketamine only in individuals treated with amphetamine (Kegeles *et al.*, 2000a; Aalto *et al.*, 2002; Kegeles *et al.*, 2002; Aalto *et al.*, 2005), suggesting that ketamine's effects may be more marked when the dopamine system is challenged. Thus, in schizophrenia NMDA hypofunction may make the dopamine system more sensitive to the effects of psychological stress.

Whilst the studies discussed above provide evidence that dopamine dysregulation in schizophrenia could be secondary to glutamatergic dysfunction, they do not identify the specific brain circuits or regions involved. The prefrontal cortex and hippocampus have both

been suggested as potential sites as both regulate midbrain dopamine neurons via glutamatergic projections to the midbrain (Christie *et al.*, 1985; Grace, 1991; Sesack and Pickel, 1992).

Hippocampus—Studies using a rodent developmental model of schizophrenia show that altered hippocampal activity is associated with increased dopamine neuron population activity, and that inactivating the hippocampus reverses the dopamine alterations (Lodge and Grace, 2006). Altered hippocampal activity is also seen in patients with schizophrenia (Heckers *et al.*, 1998; Harrison, 2004; Malaspina *et al.*, 2004) and prodromal psychosis, and has been linked to the subsequent development of schizophrenia (Schobel *et al.*, 2013). Furthermore, we recently reported in individuals with prodromal symptoms of psychosis had a negative correlation between hippocampal glutamate and striatal [18F]DOPA uptake, and this was most marked in those that went on to develop schizophrenia (Stone *et al.*, 2010).

Prefrontal cortex—Whilst there are data linking altered frontal function to striatal presynaptic dopamine dysfunction in patients and at risk subjects (Bertolino *et al.*, 2000; Meyer-Lindenberg *et al.*, 2002; Fusar-Poli *et al.*, 2011), we are not aware of any studies investigating the relationship between frontal glutamate to striatal dopamine dysfunction in patients.

There are thus several converging lines of data to suggest that glutamate dysfunction could underlie the dopamine dysfunction seen in schizophrenia and its prodrome, supporting an integrated hypothesis. However, as the data in patients are limited to date (Stone *et al.*, 2010), this requires further testing. Furthermore, it is important to note that the glutamate and dopamine systems show extensive and reciprocal interactions, and thus it may be difficult to determine which is primary, with different authorities on the subject suggesting that both glutamate and dopamine drive abnormalities in the other system (Olney and Farber, 1995; Harrison and Weinberger, 2005; Coyle, 2006; Stone *et al.*, 2007). Finally, an integrated hypothesis cannot readily explain the findings in treatment resistant patients discussed above, where glutamate dysfunction alone or other pathways may be critical.

Conclusions and Future Directions

The first decade or so of the 21st century has seen the accumulation of evidence that has allowed major refinements of the dopamine hypothesis of schizophrenia. We can now say that the major dopaminergic abnormality is presynaptic, it is present at the onset of illness and is related to the onset of psychosis. These findings appear robust: they are seen across methods and settings and, given their consistency, it would take a large body of new, contradictory evidence to bring them into doubt. Furthermore, we have plausible models of how presynaptic dopamine dysfunction might lead to the symptoms we see in the clinic, providing an explanation at both a neurobiological and clinical level. Nevertheless there are important limitations to our current understanding, in particular of how the dopamine changes might account for negative and cognitive symptoms. The 21st century has also seen continued empirical support for the glutamate hypothesis, with several converging lines of evidence indicating that a glutamatergic abnormality could underlie schizophrenia. However, whilst there have been undoubted advances in understanding the nature of glutamate

dysfunction in schizophrenia, at present there are some inconsistencies and this has not led to significant advances in treatment. This should not be surprising given the lessons from the imaging studies of the dopamine system in schizophrenia, in particular that it takes time (more than two decades in the case of dopamine), and the application of a variety of imaging techniques to develop a clear understanding of the nature of the dysfunction affecting a system. Given the limitations of current approaches to imaging glutamate using MRS, progress requires the development of new methods to image the glutamate system. Notwithstanding these caveats, there are two possible explanations for the involvement of both dopamine and glutamate in schizophrenia. One is that they underlie different sub-types of the disorder, in line with the recent findings in treatment resistance. The other is an integrated hypothesis which could explain positive symptoms in terms of presynaptic dopamine, and negative and cognitive symptoms in terms of glutamate. Of course these are not mutually exclusive. Both possibilities require further testing in patient studies and this is likely to be needed to inform the development of new treatment approaches.

Abbreviations

↑	= significantly higher in patient group
↓	= significantly lower level in patient group
-	= no significant difference
[^{11}C]-+-PHNO-	[11C]-(+)-4-propyl-9-hydroxynaphthoxazine;
[11C]DOPA	= L-[β-^{11}C]Dihydroxyphenylalanine;
[^{123}I]IBZM-	[123I](S)-(-)-3-iodo-2-hydroxy-6-methoxy-N- [(1-ethyl-2-pyrrolidinyl)methyl]benzamide
[^{18}F]-DOPA- 6-	[^{18}F]fluoro-L-Dihydroxyphenylalanine
1H-MRS	= Proton Magnetic Resonance Spectroscopy
5-HT2A	= 5-hydoxytryptamine (also known as serotonin) receptor sub-type 2A
AMPT	alpha-methyl-para-tyrosine
BG	Basal Ganglia
Chronic	Chronic psychotic illness
D1, D2, D3	= Dopamine receptor sub-type 1, 2 and 3 respectively
DAT	= Dopamine transporter
EPSE	= Extrapyramidal side-effects
FEP	first episode psychosis
Gln	glutamine

Glu	glutamate
Glx	Glutamate+ glutamine
HC	healthy control;
Hipp	Hippocampus
L-DOPA	= L-Dihydroxyphenylalanine
M	currently taking antipsychotic medication
MF	antipsychotic free
MIST	Montreal imaging stress task
MN	antipsychotic naïve
MPFC	medial prefrontal cortex (including anterior cingulated cortex
na	not analysed
PET	= Positron Emission Tomography
sd	standard deviation
SPECT	= Single Photon Emission Tomography
Tha	Thalamus
UHR	Ultra high risk

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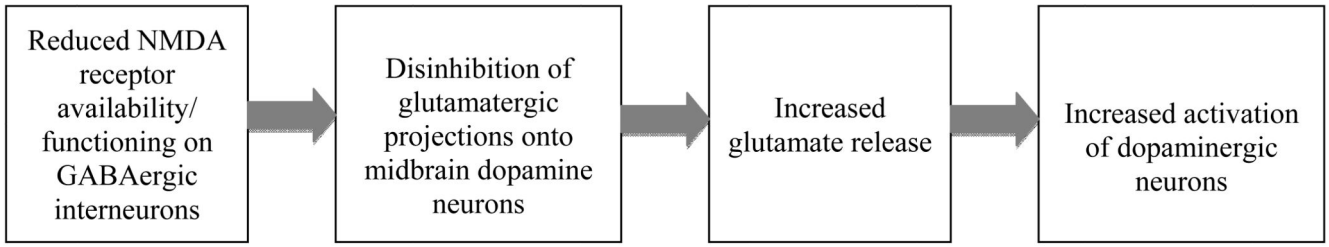

Figure 1.
Interactions between glutamatergic and dopaminergic pathways

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Table 1

The PET imaging studies of striatal dopamine synthesis capacity in schizophrenia

Study	Medication status MN/MF/M/HC	Phenotype	Radiotracer	Findings (standard effect size)
Dao-Castellana *et al.*1997	2/4/0/7	Chronic	[^{18}F]-DOPA	- (0.35)
Demjaha *et al.* 2012[d]	0/0/12/12	Chronic	[^{18}F]-DOPA	↑ (1.12)
Elkashef *et al.* 2000	0/9/10/13	Chronic	[^{18}F]-DOPA	- (-0.13)
Reith *et al.*1994	4/1/0/13	Chronic	[^{18}F]-DOPA	↑ (1.52)
Hietala *et al.*1995[a]	7/0/0/8	FEP	[^{18}F]-DOPA	- (0.9)
Hietala *et al.*1999	10/0/0/13	FEP	[^{18}F]-DOPA	↑ (1.02)
Howes *et al.* 2009	4/3/0/12	FEP/Chronic	[^{18}F]-DOPA	↑ (1.18)
Howes *et al.* 2013a[e]	5/8/16/29	Chronic	[^{18}F]-DOPA	↑ (1.14)
Kumakara *et al.* 2007[b]	3/5/0/15	Chronic	[^{18}F]-DOPA	- (0.10)
Lindstrom *et al.* 1999	10/2/0/10	FEP/Chronic	[^{11}C]-DOPA	↑ (1.01)
McGowan *et al.* 2004	0/0/16/12	Chronic	[^{18}F]-DOPA	↑ (1.55)
Meyer-Lindenberg *et al.* 2002	0/6/0/6	Chronic	[^{18}F]-DOPA	↑ (1.82)
Nozaki *et al.* 2009[c]	14/4/0/20	FEP/Chronic	[^{11}C]-DOPA	- (0.13)
Shotbolt *et al.* 2011	0/0/6/20	Chronic	[^{18}F]-DOPA	- (NA)

↑ = significantly higher in patient group; ↓ = significantly lower level in patient group; - = no significant difference

[^{11}C]DOPA= L-[β-^{11}C]Dihydroxyphenylalanine; [^{18}F]-DOPA- 6-[^{18}F]fluoro-L-Dihydroxyphenylalanine

FEP- first episode psychosis; MN- antipsychotic naïve; HC – healthy control; M – currently taking antipsychotic medication; MF- antipsychotic free

[a] Found significant difference between patients and controls found for the putamen but not striatum as a whole.

[b] Found significantly increased [^{18}F]-DOPA *turnover* in patients compared to controls.

[c] Found significantly increased uptake in left caudate nucleus but not striatum as a whole.

[d] Synthesis capacity significantly increased in the 12 responders to antipsychotic treatment but not in the treatment resistant patients

[e] Includes 14 patients and 12 controls from McGowan *et al.* 2004.

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Table 2

The PET imaging studies of dopamine release/baseline occupancy in schizophrenia

Study	Medication status MN/MF/M/HC	Phenotype	Radiotracer	Study Type	Findings (standard effect size)
Abi-Dargham *et al*. 1998[a]	2/13/0/15	13 Chronic 2 FEP	[^{123}I]IBZM	Amphetamine Induced	↑ (0.79)
Abi-Dargham *et al*. 2009[c]	6/0/0/8	FEP	[^{123}I]IBZM	Amphetamine Induced	↑ (1.32)
Breier *et al*. 1997	4/7/0/12	Chronic	[^{11}C] raclopride	Amphetamine Induced	↑ (0.88)
Laruelle *et al*. 1996	0/15/0/15	Chronic	[^{123}I]IBZM	Amphetamine Induced	↑ (0.96)
Laruelle *et al*. 1999[b]	7/27/0/36	27 Chronic 7 FEP	[^{123}I]IBZM	Amphetamine Induced	↑ (0.91)
Mizrahi *et al*. 2012	10/0/0/12	FEP	[^{11}C]-+-PHNO	MIST Induced	↑ (1.37)
Pogarell *et al*. 2012	0/8/0/7	FEP	[^{123}I]IBZM	Amphetamine Induced	↑ (1.19)
Abi-Dargham *et al* 2000	8/10/0/18	10 chronic 8 FEP	[^{123}I]IBZM	AMPT depletion	↑ (1.08)
Kegeles *et al*. 2010[d]	6/12/0/18	FEP/Chronic	[^{11}C] raclopride	AMPT depletion	- (0.63)

↑ = significantly higher in patient group; ↓ = significantly lower level in patient group; - = no significant difference

[^{123}I]IBZM - [123I](S)-(-)-3-iodo-2-hydroxy-6-methoxy-N- [(1-ethyl-2-pyrrolidinyl)methyl]benzamide; [^{11}C]-+-PHNO - [11C]-(+)-4-propyl-9-hydroxynaphthoxazine; MIST – Montreal imaging stress task

FEP- first episode psychosis; MN- antipsychotic naïve; HC – healthy control; M – currently taking antipsychotic medication; MF- antipsychotic free

[a] Abi-dargham *et al*.report a larger effect size of 1.06 as only the control group SD isincluded in their calculation (as opposed to both patient and control SDs)

[b] Includes 30pts from Laruelle *et al*. 1996 and Abi-Dargham *et al*.1998

[c] Includes patients from Abi-dargham *et al*. 2000

[d] Significant change only found for associative striatum not striatum overall

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Table 3

The PET studies of dopaminergic function in individuals at increased risk of schizophrenia

Study	Medication status MN/MF/M/HC	Phenotype	Radiotracer	Study type	Findings (standard effect size)
Bloemen *et al.* 2013[b]	14/0/0/15	UHR	[^{123}I]IBZM	Dopamine depletion	-
Howes *et al.* 2009	23/0/1/12	UHR	[^{18}F]-DOPA	Synthesis capacity	↑ (0.75)
Howes *et al.* 2011b[a]	30/0/0/29	UHR	[^{18}F]-DOPA	Synthesis capacity	↑ (1.18)
Mizrahi *et al.* 2013	12/0/0/12	UHR	[^{11}C]-+-PHNO	MIST induced dopamine release	↑ (0.98)
Suridjan *et al.* 2013	12/0/0/12	UHR	[^{11}C]-+-PHNO	D2^{high}/D3 receptor availability	-
Abi-dargham *et al.* 2004	13/0/0/13	Schizotypal	[^{123}I]IBZM	Amphetamine induced dopamine release	↑ (0.93)
Howes *et al.* 2012	16/0/0/16	Auditory hallucinations (otherwise healthy)	[^{18}F]-DOPA	Synthesis capacity	-
Huttunen *et al.* 2008	17/0/0/17	First degree relatives of patients with schizophrenia	[^{18}F]-DOPA	Synthesis capacity	↑
Shotbolt *et al.* 2011	6/0/0/20	Twins of patients with schizophrenia	[^{18}F]-DOPA	Synthesis capacity	-
Soliman *et al.* 2008[c]	16/0/0/10	"Potential schizotype"	[^{11}C] raclopride	MIST induced dopamine release	↑

↑ = significantly higher in patient group; ↓ = significantly lower level in patient group; - = no significant difference

[^{123}I]IBZM - [123I](S)-(-)-3-iodo-2-hydroxy-6-methoxy-N- [(1-ethyl-2-pyrrolidinyl)methyl]benzamide; [^{11}C]-+-PHNO - [11C]-(+)-4-propyl-9-hydroxynaphthoxazine; [^{18}F]-DOPA- 6-[^{18}F]fluoro-L-Dihydroxyphenylalanine; MIST – Montreal Imaging Stress Task; D1, D2, D3= Dopamine receptor sub-type 1, 2 and 3 respectively

MN- antipsychotic naïve; HC – healthy control; M – currently taking antipsychotic medication; MF- antipsychotic free; UHR – Ultra high risk for psychosis

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

[b] No significant differences between controls and UHR but correlation between receptor occupancy by dopamine and positive symptoms

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

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Table 4

The 1H-MRS studies in first episode schizophrenia

Study	Medication status MN/MF/M/HC	Phenotype	Field strength	Findings: Glu/Gln/Glx			
				MPFC	Hipp	Tha	BG
Aoyama *et al.* 2011[a]	17/0/0/17	FEP	4.0T	-/-/na		-/↑/na	
Bartha *et al.* 1997	10/0/0/10	FEP	1.5T	-/↑/na			
Bartha *et al.* 1999	11/0/0/11	FEP	1.5T		-/-/na		
Bustillo *et al.* 2010	14/0/0/10	FEP	4.0T	-/-/na		-/-/na	
de la Fuente Sandoval *et al.* 2011[b]	36/0/0/40	FEP/UHR	3.0T				↑/na/-
de la Fuente Sandoval *et al.* 2013	24/0/0/18	FEP	3.0T				↑/na/↑
Galinska *et al.* 2009	1/0/29/19	FEP	1.5T		na/na/-	na/na/-	
Goto*et al.* 2012 [c]	16/18	FEP	3.0T				na/na/↑
Olbrich *et al.* 2008	0/0/7/16	FEP	2.0T		-/-/na		
Théberge *et al.* 2002	21/0/0/21	FEP	4.0T	-/↑/na		-/↑/na	

1H-MRS= Proton Magnetic Resonance Spectroscopy; MN- antipsychotic naïve; M – currently taking antipsychotic medication; HC – healthy control;FEP- first episode psychosis

Tha – Thalamus; BG – Basal Ganglia; Hipp – Hippocampus; MPFC – medial prefrontal cortex (including anterior cingulated cortex; Glx – Glutamate+ glutamine; Glu – glutamate; Gln – glutamine

↑ = significantly higher in patient group;v ↓ = significantly lower level in patient group; - = no significant difference; na – not analysed; UHR – Ultra high risk for psychosis

[a] 12 patients previously reported in Théberge *et al.* 2002

[b] Subjects consist of 18 FEP and 18 UHR

[c] The number of medicated vs. unmedicated patients is not clearly described.

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Table 5

The 1H-MRS studies in studies in individuals at increased risk of schizophrenia

Study	Medication status MN/MF/M/HC	Phenotype	Field Strength	Findings: Glu/Gln/Glx			
				MPFC	Hipp	Tha	BG
Keshavan *et al.* 2009	40/0/0/46	UHR	1.5T	na/na/-		na/na/-	na/na/-
Tandon *et al.* 2008	15/0/0/14	UHR	3.0T	-/na/-			
Stone *et al.* 2009	19/3/2/27	UHR	3.0T	-/↑/-	-/-/-	↓/-/↓	
Yoo *et al.* 2009	22/0/0/22	UHR	1.5T	na/na/-		na/na/-	
Lutkenhoff *et al.* 2010	12/0/0/21	Twins of Scz patients	3.0T	↓/na/na	-/na/na		
Tandon *et al.* 2013	23/0/0/24	Children of Scz parents	1.5T	na/na/-		na/na/↑	na/na/↑
Tibbo *et al.* 2004[a]	20/0/0/22	Children of Scz parents	3.0T	na/na/na			

1H-MRS= Proton Magnetic Resonance Spectroscopy; MN- antipsychotic naïve; M – currently taking antipsychotic medication; HC – healthy control; Scz - Schizophrenia

Tha – Thalamus; BG – Basal Ganglia; Hipp – Hippocampus; MPFC – medial prefrontal cortex (including anterior cingulated cortex; Glx – Glutamate+ glutamine; Glu – glutamate; Gln – glutamine

↑ = significantly higher in patient group;v ↓ = significantly lower level in patient group; - = no significant difference; na – not analysed; UHR – Ultra high risk for psychosis

[a]Absolute values not reported but significantly increased glu:gln ration in MPFC of high risk group.