Drug models of schizophrenia

Hannah Steeds, Robin L. Carhart-Harris and James M. Stone

Abstract：Schizophrenia is a complex mental health disorder with positive, negative and cognitive symptom domains. Approximately one third of patients are resistant to currently available medication. New therapeutic targets and a better understanding of the basic biological processes that drive pathogenesis are needed in order to develop therapies that will improve quality of life for these patients. Several drugs that act on neurotransmitter systems in the brain have been suggested to model aspects of schizophrenia in animals and in man. In this paper, we selectively review findings from dopaminergic, glutamatergic, serotonergic, cannabinoid, GABA, cholinergic and kappa opioid pharmacological drug models to evaluate their similarity to schizophrenia. Understanding the interactions between these different neurotransmitter systems and their relationship with symptoms will be an important step towards building a coherent hypothesis for the pathogenesis of schizophrenia.

Keywords: amphetamine, cannabis, drug models, kappa opioid, ketamine, LSD, models, PCP, psilocybin, psychosis, salvia divinorum, schizophrenia, THC

Introduction

Existing antipsychotic medications have their main therapeutic effect through dopamine D2 receptor blockade [Kapur and Mamo, 2003]. Although approximately 30% of patients respond to antipsychotic treatment and enter full remission, and a further 30% show some response, around 20–30% do not respond to these medications at all [Meltzer, 1997; Mosolov *et al.* 2012], perhaps due to them having a different neuropathological basis to their condition [Stone *et al.* 2010; Egerton *et al.* 2012; Demjaha *et al.* 2012]. With the exception of clozapine, current antipsychotic medications do not show significant differences in efficacy, and are primarily differentiated by their side-effect profiles [Meltzer, 1997; Abbott, 2010; Lieberman *et al.* 2005]. Side effects can be severe, with extrapyramidal symptoms being typically problematic in typical antipsychotic drugs, and metabolic changes, leading to weight gain and type 2 diabetes, commonly occurring with atypical antipsychotic drugs [Lieberman *et al.* 2005; Langer and Halldin, 2002]. For those patients that do respond, long-term compliance is required, with attempts to discontinue medication generally leading to relapse [Langer and Halldin, 2002; Boonstra *et al.* 2011; Stefansson *et al.* 2008; Pratt *et al.*

2012]. In addition, even when effective in reducing positive symptoms, dopamine-blocking antipsychotic drugs are largely ineffective at reducing negative symptoms and cognitive impairments, and it is these domains that are the most important predictors for long-term social functioning [Langer and Halldin, 2002; Stefansson *et al.* 2008; Pratt *et al.* 2012]. There is thus a pressing need to develop novel treatments that have more tolerable side effects, and that are effective in those patients who fail to respond to currently available antipsychotic drugs. Drug models of psychosis may assist in the identification of alternative therapeutic targets and may be utilized in the development and screening of novel compounds prior to testing in patients.

The ideal model of schizophrenia would faithfully mimic the biological changes driving pathogenesis and carry high predictive value for the efficacy of novel therapeutics [Langer and Halldin, 2002]. Many drug models of schizophrenia have been investigated for this purpose, and several have shown promising results. It is important to note that, in contrast to drug models, schizophrenia is chronic, neurodevelopmental, and episodic with different symptom domains predominating at different stages.

Correspondence to:
James Stone, MBBS MRCPsych PhD
King's College London,
Institute of Psychiatry
Psychology and
Neuroscience, De
Crespigny Park, London
SE5 8AF, UK,
Imperial College London,
Division of Brain Sciences,
Du Cane Road, London
W12 0NN, UK
james.m.stone@kcl.ac.uk

Hannah Steeds, BSc
**Robin L. Carhart-Harris,
PhD**
Imperial College London,
Division of Brain Sciences,
Du Cane Road, London
W12 0NN, UK

Therefore, any purely pharmacological model is likely destined to be incomplete in the extent to which it can represent the full picture of schizophrenia.

Common discrepancies between pharmacological models and schizophrenia include an inability to faithfully mimic all of the symptom domains, insight into the fact that the symptoms were caused by a drug, and the experience of euphoria, or simply of liking the drug effects [Curran *et al.* 2009; Abi-Saab *et al.* 1998]. Furthermore, some drugs known to induce schizophrenia-like symptoms in humans do so only after continued administration (e.g. amphetamine), which make them less suitable for experimental medicine studies due to ethical concerns as well as issues with practicality and the increased risk of adverse effects. In testing novel antipsychotics against drug models of psychosis, it is also worth considering that any observed attenuation of symptoms with the antipsychotic may be due to a pharmacological interaction that is irrelevant to the biology of schizophrenia [Jones *et al.* 2011].

Animal models of psychosis have some advantages for testing novel agents, as chronic and perinatal dosing regimens are possible, but they are difficult to interpret unless they have been extensively cross-validated with human models. All of the primary symptoms of schizophrenia, such as hallucinations, delusions and thought disorder, require verbal report for their measurement in order to be properly tested and measured, and it is not always clear how relevant animal-based biomarkers are to the uniquely human symptoms of schizophrenia. Furthermore, putative therapeutic agents do not always have the same effects in animals as in man [Pratt *et al.* 2012; Curran *et al.* 2009; Jones *et al.* 2011].

Several drugs induce effects that resemble at least some of the symptoms of schizophrenia in animals and man [Curran *et al.* 2009; Jones *et al.* 2011; Marcotte *et al.* 2001]. In this review, we investigate the relative strengths of dopaminergic, glutamatergic, serotonergic, endocannabinoid, GABAergic, cholinergic and kappa-opioid pharmacological models of schizophrenia, comparing neurochemical findings in schizophrenia supporting the models, considering the effects of the candidate drugs in humans and contrasting evidence from animal models.

Pharmacological models of schizophrenia

Dopaminergic

The relationship between the clinical effective dose of antipsychotic drugs and their affinity for the D2 receptor has been established for more than 30 years [Seeman and Lee, 1975; Kapur *et al.* 2005]. Patients with schizophrenia have been shown to have evidence of abnormal dopaminergic function, with increased dopamine release following amphetamine administration, elevated synaptic dopamine and increased [18F] DOPA uptake [Laruelle *et al.* 1996, 2003; Kegeles *et al.* 2002, 2010; Abi-Dargham *et al.* 2009; Howes *et al.* 2012]. The dopaminergic theory of aberrant salience provides an explanation for some of the positive delusional symptoms of psychosis due to overactive mesolimbic dopaminergic transmission [Kapur *et al.* 2005; Seeman, 1987; Seeman and Kapur, 2000]. In contrast, it has been suggested that an underactive dopamine system in the frontal cortex may underlie some of the negative symptoms [Davis *et al.* 1991].

The psychostimulants amphetamine and cocaine increase synaptic levels of dopamine, and have been reported to exacerbate psychotic episodes in people with existing schizophrenia [Farren *et al.* 2000; Bramness *et al.* 2012]. In early studies of amphetamine administration in healthy volunteers, large single oral doses were found to induce an acute psychosis [Angrist and Gershon, 1970; Bell, 1973]. However, at lower doses, paranoid and other psychotic symptoms emerge only with repeated dosing, and only in some individuals. It has been suggested that amphetamines may act as a stressor to induce psychosis in a vulnerable subset of the population [Bramness *et al.* 2012].

Positive symptoms induced by amphetamines and cocaine include auditory hallucinations, thought disorder and grandiose delusions, and chronic amphetamine users have been found to score highly on the Positive and Negative Syndrome Scale (PANSS) [Angrist and Gershon, 1970; Harris and Batki, 2000; Wolkin *et al.* 1994; Angrist *et al.* 1974]. However, in a recent survey of effects associated with amphetamine use, we found that schizophrenia-like effects were relatively rare in regular users, and that experienced users ranked amphetamine behind ketamine and alcohol in terms of its propensity to cause thought disorder, and behind cannabis, psilocybin and ketamine in terms of likelihood of inducing

hallucinations and delusions [Carhart-Harris *et al.* 2013a].

In rodents, administration of dopaminergic stimulants has been reported to induce repeated ('stereotyped') behaviours, such as locomotion, sniffing and chewing, that may be related to the positive symptoms of psychosis, as well as to impaired prepulse inhibition (PPI), a marker of sensory gating impairment also seen in patients with schizophrenia [Segal and Mandell, 1974]. With chronic dosing, the PPI and stereotyped behaviours occur at increasing frequency and duration over time [Segal and Mandell, 1974]. This phenomenon is termed 'sensitization' and some groups have suggested that sensitization shares common mechanisms with the development of psychosis in man [Ujike, 2002; Featherstone *et al.* 2007]. This induced state has been linked to: (1) changes in the inhibitory dopamine D3 receptor function (possibly by down-regulating their availability for stimulation); (2) altered dopamine transmission in the nucleus accumbens; and (3) increases in total D2 receptor dimerization [Wang *et al.* 2010; Richtand *et al.* 2001]. As in patients with schizophrenia, sensitized rats show an enhanced dopamine release in response to amphetamine compared with controls, and some limited but long-term cognitive impairments have also been reported in attention and set-shifting which are features of schizophrenia [Tenn *et al.* 2003; Fletcher *et al.* 2005]. Amphetamine-induced sensitization is commonly used as a model for the positive symptoms of schizophrenia but it is not thought to fully resemble the cognitive and negative symptom domains [Jones *et al.* 2011; Wang *et al.* 2010]. Furthermore, purely dopaminergic models are likely to lead to the development of more dopamine-targeting antipsychotic drugs, which may be unlikely to lead to a great improvement in efficacy or safety. Thus, alternative models are of interest for the identification of novel drug targets.

Glutamatergic

The NMDA receptor hypofunction hypothesis of schizophrenia has been suggested as an alternative or additional neurochemical model of schizophrenia to the dopamine hypothesis [Olney and Farber, 1995; Goff and Coyle, 2001]. Glutamate signalling plays an important role in synaptic plasticity and cortical processing in the brain and genetic studies have implicated abnormalities in this system as possible drivers of pathogenesis in schizophrenia [Schwartz *et al.* 2012]. It has also been suggested that glutamate-driven excitotoxicity could underlie reductions in grey matter volume seen in schizophrenia [Olney and Farber, 1995; Okugawa *et al.* 2007; Hertzmann *et al.* 1990]. Although there is little direct evidence of NMDA receptor hypofunction in schizophrenia, one imaging study using an NMDA receptor single photon emission tomography tracer reported a reduction in NMDA receptor binding in medication free patients with schizophrenia [Pilowsky *et al.* 2006]. Similarly, NMDA receptor NR1 subunit mRNA has been reported to be reduced in post-mortem patients with schizophrenia [Law and Deakin, 2001].

The dissociative anaesthetics phencyclidine (PCP) and ketamine are both uncompetitive NMDA receptor antagonists suggested to be pharmacological models of schizophrenia [Laruelle *et al.* 2000]. They have been shown to lead to increases in the power of gamma oscillations [Rotaru *et al.* 2012], increases in functional connectivity [Driesen *et al.* 2013], and increases in prefrontal glutamate (or glutamine) levels, demonstrated both in animal microdialysis studies, and in human proton magnetic resonance spectroscopy (^{1}H-MRS) studies [Moghaddam *et al.* 1997; Rowland *et al.* 2005; Stone *et al.* 2012a]. The mechanism by which they lead to these changes is still controversial, although it has been shown that NMDA receptor inhibition leads to a reduction in GABAergic interneuron function, possibly through preferential effects of ketamine on NMDA receptors expressed on these cells [Homayoun and Moghaddam, 2007]. This has been suggested to lead to increases in pyramidal cell firing due to disinhibition [Olney and Farber, 1995]. Recent work suggests that the preferential blockade of NMDA receptors on cortical GABAergic interneurons is unlikely to occur, however, with more evidence for a preferential sensitivity of pyramidal cell NMDA receptors to ketamine [Rotaru *et al.* 2012]. One intriguing possibility is that reductions in GABAergic interneuron function may be mediated by the generation of brain superoxide, since inhibiting superoxide levels prevented reductions in interneuron activity following ketamine administration [Behrens *et al.* 2007]. Furthermore, inhibition of the formation of reactive oxygen species prevents the psychosis-like effects of NMDA receptor blockade in animal models [Sorce *et al.* 2010; Levkovitz *et al.* 2007; Zhang *et al.* 2007; Monte *et al.* 2013].

Ketamine has been demonstrated to exacerbate positive and negative symptoms in pre-existing schizophrenia [Lahti *et al.* 1995b] and, in some patients, use has been linked to impairment in cognition, specifically by inducing a larger deficit in recall memory in people with schizophrenia compared to controls [Malhotra *et al.* 1997; Lahti *et al.* 1995a]. Acute doses of ketamine in healthy volunteers induce schizophrenic-like positive and negative symptoms, and may also lead to impairments in cognitive function that resemble schizophrenia [Stone *et al.* 2012a; Krystal *et al.* 2005; Morgan *et al.* 2004; Deakin *et al.* 2008]. Ketamine binding to NMDA receptors has been reported to correlate with its effect on negative symptoms [Stone *et al.* 2008] whereas downstream effects of ketamine, including increases in ^{1}H-MRS-measured prefrontal glutamate levels and ketamine-induced changes in functional magnetic resonance imaging (fMRI) signal, correlated with ratings of positive psychotic symptoms [Stone *et al.* 2012a; Deakin *et al.* 2008], suggesting that different symptom clusters may have distinct underlying mechanisms.

There are several dissimilarities between the ketamine-induced state and schizophrenia [Steen *et al.* 2006]. For example, auditory hallucinations are one of the most common symptoms in schizophrenia, but the hallucinations and illusions experienced following acute administration of ketamine are more commonly visual [Abi-Saab *et al.* 1998; Steen *et al.* 2006]. On this basis, it has been suggested that, rather than modelling chronic schizophrenia, acute ketamine administration may induce a state closer to the prodrome/ early stages of schizophrenia, when fleeting visual changes of the type that occur following ketamine administration have also been reported to occur [Klosterkotter *et al.* 2001; Corlett *et al.* 2007].

Another criticism of acute ketamine or PCP administration is that it is unlikely to be able to replicate the neurobiological changes that occur over time in the schizophrenic brain [Malhotra *et al.* 1997; Tsai and Coyle, 2002]. Thus, there has been considerable interest in the long-term effects of these drugs. Some chronic PCP and ketamine users have been found to have persistent schizophrenia-like symptoms [Jentsch and Roth, 1999; Krystal *et al.* 1994], and such patients may present with a symptomatic profile that can so closely resemble schizophrenia that it may even be misdiagnosed as such [Abi-Saab *et al.* 1998; Javitt, 1987]. Reported symptoms in chronic PCP and

ketamine users may include paranoid delusions, persistent cognitive deficits and, in chronic PCP users, there have been reports of a greater incidence of auditory than visual hallucinations [Jentsch and Roth, 1999]. Depressive and dissociative symptoms also increase with persistent use of ketamine in chronic users [Morgan *et al.* 2004].

Biochemical brain changes that are similar to those seen in patients with schizophrenia have been found in chronic ketamine and PCP users. Dopamine D1 receptors are upregulated in the frontal cortex of patient with schizophrenia and in chronic ketamine users [Narendran *et al.* 2005]. This upregulation is associated with cognitive impairment and dopaminergic hypofunction [Narendran *et al.* 2005]. Chronic ketamine users have also been found to have other brain imaging changes associated with schizophrenia including reduced thalamic NAA [Stone *et al.* 2014b], and reduced prefrontal grey matter volume [Liao *et al.* 2011]. Furthermore, chronic PCP users have been found to have decreased blood flow in the frontal cortex, similar to that seen in schizophrenia [Hertzmann *et al.* 1990].

In animal models, NMDA receptor antagonists induce behavioural, locomotor and cognitive changes, and chronic administration also induces neurobiological changes similar to those found in the brains of schizophrenia patients [Jones *et al.* 2011; Jentsch and Roth, 1999]. Primates given a chronic infusion of PCP display scanning and pacing behaviours and rodents develop deficits in motor planning, working memory and stereotypies [Linn *et al.* 1999]. These symptoms can be attenuated, but not abolished completely, with antipsychotic medication, which may suggest something of their underlying neurobiology [Steinpreis *et al.* 1994]. Importantly, chronic administration of PCP may be a useful means to study similar degeneration to that seen in the brains of schizophrenia patients because it also induces cortical neurodegenerative changes in rats [Olney and Farber, 1995; Wang and Johnson, 2005]. This effect can be blocked by AMPA receptor antagonists and so it may be that excess glutamate release is driving neurotoxicity in the model [Olney and Farber, 1995; Deutsch *et al.* 2001]. In rodents with chronic PCP treatment, PPI is disrupted, dopaminergic transmission in the frontal lobe is reduced and changes in the mesolimbic and frontal–cortical dopamine systems mimic those of schizophrenia [Jones *et al.* 2011; Jentsch and Roth, 1999]. Chronic neonatal

administration of PCP induces lasting cognitive deficits and increases in putative animal equivalents of positive symptoms [Stefani and Moghaddam, 2005; Uehara *et al.* 2010]. Furthermore, in primate models, these neurobiological changes persist beyond the acute effects of the drug and behavioural and cognitive deficits can still be seen after PCP administration has been stopped [Olney and Farber, 1995; Jentsch *et al.* 1997].

The models generated by the use of dissociative anaesthetics demonstrate that NMDA receptor dysfunction could be a key factor in the pathogenesis of schizophrenia [Olney and Farber, 1995; Laruelle *et al.* 2000; Javitt and Zukin, 1991]. NMDA receptor antagonist models of schizophrenia could have value in predicting the efficacy of much needed therapies that target the cognitive and negative symptom domains of the illness because of their evident interaction with areas of cognition relevant to schizophrenia [Laruelle *et al.* 2000; Neill *et al.* 2010]. It should be borne in mind, however, that these drugs are known to act on multiple neurotransmitter systems in the brain including dopamine [Jentsch *et al.* 1997; Kapur and Seeman, 2002], and this may be central to their generation of a more complete clinically picture of schizophrenia than those that act primarily on a single neurotransmitter system.

Serotonergic

Although less widely studied than dopamine or glutamate, there is evidence that the serotonin (5-HT) system may also be involved in psychotic symptom formation. Support comes from the observation that hallucinogens such as LSD and psilocybin are 5-HT_{2A} receptor agonists [Vollenweider and Geyer, 2001]. These drugs induce psychopathologies which include agitation, anxiety, visual hallucinations and illusions, which are similar to symptoms seen in the first psychotic episode of the illness [Fletcher and Honey, 2006; Hyde *et al.* 1978]. Furthermore, these drugs disrupt PPI through direct stimulation of the 5-HT_{2A} receptors [Quednow *et al.* 2012; Aghajanian and Marek, 2000], lead to a blending of the brain networks engaged during rest and active task performance [Carhart-Harris *et al.* 2013b], and lead to downstream increases in glutamate release [Scruggs *et al.* 2003; Muschamp *et al.* 2004], closely resembling effects seen in patients with psychosis. It is interesting to note that blockade of 5-HT_{2A} receptors inhibits the

effects of NMDA receptor antagonists, suggesting that at least some of the psychosis-like effects of NMDA receptor antagonism may be mediated via serotonergic mechanisms [Aghajanian and Marek, 2000; Breese *et al.* 2002].

Many atypical antipsychotics such as clozapine, risperidone and olanzapine are 5-HT_{2A} receptor antagonists, having higher affinity for 5-HT_{2A} receptors than for dopamine D_2 receptors [Jentsch and Roth, 1999; Williams *et al.* 1997; Meltzer, 1996]. It is unclear to what extent these properties are involved in their antipsychotic effect, however. 5-HT2A receptor antagonists have been suggested to be potentially useful in improving cognition or negative symptoms in patients with schizophrenia [Akhondzadeh *et al.* 2008; Roth *et al.* 2004], but trials of 5-HT2A antagonists for schizophrenia to date have not progressed beyond phase III due to lack of efficacy against positive symptoms [de Paulis, 2001; Ebdrup *et al.* 2011].

There are several differences between the symptoms of schizophrenia and the hallucinogenic state induced by serotonergic drugs [Corlett *et al.* 2009]. With serotonergic drugs, subjects tend to experience hallucinations which are generally visual, and so not typical of established schizophrenia, although they may resemble symptoms that occur in the early phase of psychosis [Klosterkotter *et al.* 2001; Geyer and Vollenweider, 2008]. Perceptions and expectations of the action of these drugs can also alter the subsequent psychedelic experience and this means that the effects of the drugs can be unpredictable for different subjects, possibly making it a model that is difficult to reliably reproduce [Corlett *et al.* 2009]. Nonetheless, schizophrenia-like states can be observed in people while on these drugs and altered activity in the prefrontal cortex results in mild thought disorder and altered perception which are similar to that seen in schizophrenia [Carter *et al.* 2005; Strassman *et al.* 1994; Carhart-Harris *et al.* 2012]. Furthermore, individuals with a family history of schizophrenia appear to be at greater risk of schizophreniform symptoms following LSD [Vardy and Kay, 1983], and it has been suggested that LSD use may lead to an earlier onset of schizophrenia [Breakey *et al.* 1974].

Many studies have shown that humans and rodents can develop tolerance to psychedelics and so this model may be limited in the extent to which it can represent the long-term neurobiological changes that characterize the schizophrenic brain

[Marcotte *et al.* 2001]. However, a recent study has shown that chronic administration of lower doses of LSD in rodents can induce a behavioural syndrome that persists after the drug is stopped [Marona-Lewicka *et al.* 2011]. Symptoms from this chronic administration include irritability, hyper-sensitivity to noise, anhedonia, social withdrawal and locomotor changes, which can be reduced by the administration of antipsychotic drugs [Marona-Lewicka *et al.* 2011].

Endocannabinoid

Manipulation of the endocannabinoid system provides another possible way to model schizophrenic-like symptoms. The primary active component of cannabis, delta-9 tetrahydrocannabinol (THC) is an agonist of the cannabinoid receptor CB_1. Its mechanism of action is not fully understood but binding of this molecule may act downstream of dopamine release and play a regulatory role in several neurotransmitter systems [Kuepper *et al.* 2010; Koethe *et al.* 2009]. The endocannabinoid system plays a role in attention, learning and memory and so dysregulation of this system could plausibly be another contributor to the pathogenesis of schizophrenia [Fernandez-Espejo *et al.* 2009; Solowij and Michie, 2007].

Acute cannabis or THC administration may induce positive and negative symptoms as well as cognitive impairments resembling those of schizophrenia in healthy individuals, and may also exacerbate the symptoms of schizophrenia in those already affected by the condition [Koethe *et al.* 2009; Morrison *et al.* 2009; Morrison and Stone, 2011; D'Souza, 2007; D'Souza *et al.* 2004, 2005; Stone *et al.* 2014a]. Cannabis administration is associated with changes in neurophysiological measures that resemble those seen in patients with schizophrenia including P50 suppression, mismatch negativity and the P300 potential [Gallinat *et al.* 2012]. THC has also been shown to modulate binocular depth perception, in a manner that resembles changes seen in prodromal psychosis and schizophrenia [Koethe *et al.* 2006]. THC-induced psychotic symptoms have been shown to be associated with disruption of coherence between frontal theta brain activity [Morrison *et al.* 2011], and with changes to the normal pattern of brain activity preceding conscious action [Stone *et al.* 2012b; Ford *et al.* 2002, 2007]. Disruptions of brain activity prior to the onset of willed action have also been demonstrated in patients with schizophrenia, and are suggested to underlie impairments in efference copy generation, leading to misrecognition of self-generated actions as arising from an external source [Stone *et al.* 2012b; Ford *et al.* 2002].

Rodent and primate THC models mimic some of the cognitive impairments seen in schizophrenia. For example, a dose-dependent impairment in spatial working memory has been reported in adult rhesus monkeys following THC administration and the effect is more marked when THC is administered in adolescence when the brain is more vulnerable to chemical interference [Verrico *et al.* 2012]. Working memory dysfunction, impaired PPI and persisting behavioural changes with underlying neurobiological changes following adolescent exposure, have been observed in rodents following THC treatment, effects that could be symptomatically controlled with antipsychotic agents given to adult rats [Realini *et al.* 2009; Rubino *et al.* 2008; Schneider and Koch, 2003].

Further support for endocannabinoid models of psychosis comes from research using cannabidiol (CBD). Although it has relatively low affinity for CB1 and CB2 receptors in displacement studies, cannabidiol appears to act as noncompetitive antagonist of both CB1 and CB2 receptors at relatively low concentrations when studied *in vivo*, although the mechanism by which this occurs has still not been fully elucidated [Thomas *et al.* 2007]. CBD has been reported to have anxiolytic and antipsychotic properties, with a recent double-blind placebo-controlled study in patients with early stage schizophrenia reporting efficacy *versus* psychotic symptoms of similar magnitude to existing antipsychotic agents, but with a lower incidence of side effects [Leweke *et al.* 2012]. This suggests that the symptoms of schizophrenia may emerge, at least in part, through activation of CB1 and/or CB2 receptors, and CBD may inhibit this effect. Interestingly, CBD has been reported to reduce the psychomotor activating effects of ketamine, with a trend to reduce ketamine-induced depersonalization [Hallak *et al.* 2011], suggesting that some of the downstream effects of NMDA receptor blockade may be mediated by the endocannabinoid system.

GABAergic

There is a growing body of evidence for the dysfunction of GABAergic neurons in schizophrenia and, as gamma-aminobutyric acid (GABA) signalling interacts very closely with glutamatergic

and dopaminergic, models of GABAergic dysfunction may help to unify our understanding of schizophrenia [Pratt *et al.* 2012]. Post-mortem studies have found differences in GABA receptor subunit expression and reduced GABAergic cell types in the brains of schizophrenic patients [Pratt *et al.* 2012]. It is also known that the GABA system undergoes changes during adolescence and that this is a time where patients commonly begin to show symptoms of schizophrenia [Lewis *et al.* 1999]. Furthermore GABAergic firing regulates dopamine transmission in the prefrontal cortex and a GABA interneuron deficit in schizophrenia has been proposed to underlie some of the clinical symptoms [Lewis *et al.* 1999; Japha and Koch, 1999]. GABA-A antagonists disrupt PPI when injected into the rodent medial prefrontal cortex through their action on the dopaminergic system, an effect which can be reversed with D2-blocking antipsychotic drugs [Japha and Koch, 1999]. In a related theory (arising from the methylazoxymethonol acetate rodent model of schizophrenia), Lodge and Grace hypothesized that increased hippocampal glutamatergic outputs, arising secondary to reductions in hippocampal parvalbumin staining GABAergic interneurons in schizophrenia, drive increased striatal dopamine activity [Lodge and Grace, 2011; Gill *et al.* 2011]. Grace and collaborators subsequently showed that a novel positive allosteric modulator of the alpha-5 subunit of GABA-A receptors reduced hyperactive locomotor response and spontaneously active VTA dopamine neurons in this model [Gill *et al.* 2011], suggesting that normalization of hippocampal GABAergic function might be a valid approach to antipsychotic drug development.

There is some evidence that GABA-A receptor manipulation affects psychotic symptoms on humans. In a recent study, the benzodiazepine receptor antagonist iomazenil led to worsening of psychotic symptoms and perceptual alterations in patients with schizophrenia, but not controls [Ahn *et al.* 2011]. In healthy volunteers, the combination of iomazenil with m-cholorphenylpiperizine (m-CPP), a partial agonist of 5-HT2A/2C receptors, has also been shown to lead to perceptual disturbances and other effects suggested to resemble psychosis [D'Souza *et al.* 2006]. In contrast, the psychoactive component of the fly agaric mushroom, muscimol, is a potent GABA-A receptor agonist, and this, and other, GABA-A agonists have generally been found to lead to confusion in healthy volunteers, and worsening of schizophrenia in patients, possibly through preferential action at presynaptic receptors [Meldrum, 1982; Yamamoto *et al.* 2011].

Although there is considerable interest in the potential for novel drugs targeting GABA neurotransmission in schizophrenia [Rudolph and Knoflach, 2011], results from existing compounds in patients have not been promising [Rudolph and Knoflach, 2011; Buchanan *et al.* 2011]. It is hoped that novel approaches to this system may yield additional benefit [Rudolph and Knoflach, 2011].

Cholinergic
There has been considerable interest in both nicotinic and muscarinic neurotransmission in schizophrenia.

Nicotinic. It is well recognized that patients with schizophrenia have a much higher use of tobacco than other patients with mental illness, and it was hypothesized that this may be in an effort to self-medicate and reduce some of the negative and cognitive symptoms of the illness [Ripoll *et al.* 2004]. Patients with schizophrenia have been reported to have reduced alpha-4 and alpha-7 nicotinic receptor brain expression in post-mortem studies [Ripoll *et al.* 2004], and nicotine has been reported to improve PPI in NMDA receptor antagonist models of psychosis [Domino *et al.* 2004; Levin *et al.* 2005], although nicotine did not attenuate ketamine effects in humans [D'Souza *et al.* 2012]. A number of alpha-7 nicotinic agonists have been developed for use in patients with schizophrenia, and early trials have shown promising results on cognitive and negative symptoms [Lieberman *et al.* 2013; Freedman *et al.* 2008].

Although nicotinic antagonists are generally used as muscle relaxants and are not thought to have any effects on mental state, the centrally acting drug bupropion has some effect on inhibiting nicotinic receptors and has also been reported that it may be associated with the development of psychotic symptoms [Kumar *et al.* 2011]. However, given its rich pharmacology, including actions as a dopamine and noradrenaline reuptake inhibitor [Arias *et al.* 2009], it is questionable whether nicotinic receptor antagonism is involved in this effect. Furthermore, Varenicline, a partial agonist at alpha-4 nicotinic receptors, and a full agonist at alpha-7 nicotinic receptors [Mihalak *et al.* 2006], has been reported to have no significant effect in

worsening psychotic symptoms in patients with schizophrenia, with only 5% of patients reporting an increase in symptoms [Cerimele and Durango, 2012]. It thus seems that nicotinic receptor antagonism does not reliably induce or worsen positive psychotic symptoms, and due to the systemic effects of full nicotinic receptor antagonists, it is unlikely nicotinic antagonists would be useful to model for cognitive impairment in schizophrenia.

Muscarinic. Blockade of acetylcholine receptors with atropine, scopolamine and other drugs have been reported to lead to delirium and hallucinations (generally visual) [Perry and Perry, 1995], as well as cognitive impairments [Minzenberg *et al.* 2004; Klinkenberg and Blokland, 2010], and it has been suggested that antimuscarinic drugs may induce a syndrome closely related to schizophrenia [Barak, 2009].

Unmedicated first episode patients with schizophrenia have been reported to have reduced muscarinic receptor availability [Raedler *et al.* 2003], and clozapine has higher occupancy of muscarinic receptors than olanzapine [Raedler, 2007]. It is possible that this binding may underlie some of clozapine's enhanced efficacy, as has been shown to be an M1/M4 partial agonist, and another drug (xanomeline) sharing this property has been reported to show antipsychotic efficacy *versus* positive and negative symptoms, as well as improvements in measures of cognition in early clinical trials [Mirza *et al.* 2003; Shekhar *et al.* 2008]. Problems with cholinergic side effects from xanolemine have led to high levels of dropout from these studies, however [Mirza *et al.* 2003]. Scopolamine has been used to model cognitive impairments [Klinkenberg and Blokland, 2010], and it seems reasonable that these drug-induced effects may have a similar neurochemical basis to those occurring in schizophrenia, and so could provide a target for the development of novel agents to improve cognition in affected patients [Barak and Weiner, 2011].

Kappa opioids
Salvia divinorum is a kappa opioid agonist, which is becoming more commonly used as a recreational drug, and which leads to potent symptoms of dissociation and complex and vivid hallucinations (visual, tactile and auditory) [Johnson *et al.* 2011; Lange *et al.* 2010; Ranganathan *et al.* 2012]. However, the effects of salvia divinorum may not be particularly representative of schizophrenic psychosis, since participants describe entering other realms and meeting entities or beings [MacLean *et al.* 2013] and this is rarely reported in schizophrenia. Although long-term effects have not generally been reported, there is one case report of an individual developing schizophreniform psychosis following exposure to salvia divinorum [Przekop and Lee, 2009].

There has been some suggestion that kappa opioid receptors may be abnormally distributed in the hippocampus in patients with schizophrenia, and that cerebrospinal fluid (CSF) level of dynorphins, the endogenous peptide ligands for kappa opioid receptors, may correlate with symptomatology and response to antipsychotic treatment [Tejeda *et al.* 2012]. However, research studies into the kappa opioid system in schizophrenia have been relatively small in scale, and further work is required [Tejeda *et al.* 2012].

Convergence of models via prefrontal glutamate
Several of these proposed models, in particular, acute NMDA receptor blockade, $5HT_{2A}$ agonism, THC administration and amphetamine administration, have all been reported to increase synaptic glutamate levels in prefrontal cortex (either measured directly by microdialysis, or estimated using ^{1}H-MRS) [Moghaddam *et al.* 1997; Rowland *et al.* 2005; Stone *et al.* 2012a; Scruggs *et al.* 2003; Muschamp *et al.* 2004; Pistis *et al.* 2002; Del Arco *et al.* 1998]. Although it has not been established whether the increased glutamate levels are associated with the psychosis-like effects of these drugs, it is interesting to note that glutamine, a marker of increased prefrontal glutamate release, has been reported in patients in the early phase of psychosis [Marsman *et al.* 2013] and, furthermore, that prefrontal glutamate levels appear to be associated with failure to achieve remission following dopaminergic antipsychotic drug treatment [Egerton *et al.* 2012; Demjaha *et al.* 2014; Szulc *et al.* 2013].

It should be noted that studies using 1H-MRS are still somewhat conflicting in terms of the metabolites affected in the medial prefrontal cortex – studies investigating response to antipsychotic drugs have generally reported associations with glutamate levels, which may represent a total pool of glutamate (both metabolic and neurotransmitter), whereas early psychosis has been associated with increased glutamine levels in the same brain

region. Furthermore, in one study in healthy volunteers ketamine was reported to increase medial prefrontal glutamine levels acutely [Rowland *et al.* 2005], whereas in a second study, ketamine increased glutamate levels subacutely [Stone *et al.* 2012a]. It is possible that estimated glutamine levels (generated following the release of glutamate as a neurotransmitter) may reflect a higher active turnover of glutamate through neurotransmission, with increased estimated glutamate concentration occurring as a downstream consequence (possibly due to more glutamate being generated secondary to the increased turnover). The only way to study this directly in humans at present is with ^{13}C MRS, which, although a powerful approach, is costly and limited in resolution [Rothman *et al.* 2011; Ramadan *et al.* 2013].

Conclusion

Dopaminergic psychostimulants provide a good model of the paranoid psychosis of schizophrenia but do not accurately mimic the cognitive or negative symptom domains [Pratt *et al.* 2012]. Use of dopaminergic models to predict the efficacy of novel therapeutics is likely to select only the medications that primarily act on dopamine transmission. In contrast, NMDA receptor antagonists and THC both generate a more complete model of schizophrenia, including aspects of the positive, negative and frontal cognitive symptoms [Krystal *et al.* 1994; Morrison *et al.* 2009; Morrison and Stone, 2011; D'Souza *et al.* 2004]. Chronic administration of THC and NMDA receptor antagonists in animal models also induce neurobiological changes similar to those seen in schizophrenia and their action on several overlapping neurotransmitter systems means that these drugs could give more insight into the complex clinical condition.

While much research has been done into the role of dopamine, glutamate and cannabis in schizophrenia, other models may also have value with further investigation. Serotonergic hallucinogens model some aspects of prodromal and first episode psychosis in humans and chronic low doses in animal models seem to be able to mimic more symptom domains [Marona-Lewicka *et al.* 2011]. Furthermore, although drugs affecting GABAergic and cholinergic receptors are less likely to directly induce psychosis-like effects in healthy volunteers, there is a substantial amount of evidence for these neurotransmitter systems being altered in patients with schizophrenia. Drugs targeting GABA and acetylcholine receptors may still prove to be a promising avenue for novel treatments in schizophrenia [Rudolph and Knoflach, 2011; Foster *et al.* 2012].

The development of translational animal models based on findings from human studies is important for the rapid testing of novel antipsychotic agents. Objective measurements for different symptoms have already begun to show promise in being able to predict the therapeutic efficacy of new antipsychotics and could give key insight into the effects of abnormalities in specific brain circuitry in schizophrenia [Curran *et al.* 2009].

While pharmacological models may never be able to accurately mimic all aspects of such a complex condition as schizophrenia, they may still be able to provide valuable insight into the neurobiological mechanisms underlying specific symptom domains [Curran *et al.* 2009]. Targeting individual neurotransmitter systems has highlighted the extent to which these systems interact and understanding these links will be an important step towards building a single coherent hypothesis for the pathogenesis of schizophrenia [Japha and Koch, 1999]. It is hoped that new developments in this field will generate new understanding of the biological underpinnings of schizophrenia and so facilitate the development of improved therapeutics [Abbott, 2010; Curran *et al.* 2009].

Funding

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

Abbott, A. (2010) Schizophrenia: The drug deadlock. *Nature* 468: 158–159.

Abi-Dargham, A., van de Giessen, E., Slifstein, M., Kegeles, L. and Laruelle, M. (2009) Baseline and amphetamine-stimulated dopamine activity are related in drug-naive schizophrenic subjects *Biol Psychiatry* 65: 1091–1093.

Abi-Saab, W., D'Souza, D., Moghaddam, B. and Krystal, J. (1998) The NMDA antagonist model for schizophrenia: promise and pitfalls. *Pharmacopsychiatry* 31(Suppl. 2): 104–109.

Aghajanian, G. and Marek, G. (2000) Serotonin model of schizophrenia: emerging role of glutamate mechanisms. *Brain Res Brain Res Rev* 31: 302–312.

Ahn, K., Gil, R., Seibyl, J., Sewell, R.A. and D'Souza, D.C. (2011) Probing GABA receptor function in schizophrenia with iomazenil. *Neuropsychopharmacology* 36: 677–683.

Akhondzadeh, S., Malek-Hosseini, M., Ghoreishi, A., Raznahan, M. and Rezazadeh, S. (2008) Effect of ritanserin, a 5HT2A/2C antagonist, on negative symptoms of schizophrenia: a double-blind randomized placebo-controlled study. *Prog Neuropsychopharmacol Biol Psychiatry* 32: 1879–1883.

Angrist, B. and Gershon, S. (1970) The phenomenology of experimentally induced amphetamine psychosis - preliminary observations. *Biol Psychiatry* 2: 95–107.

Angrist, B., Sathananthan, G., Wilk, S. and Gershon, S. (1974) Amphetamine psychosis: behavioral and biochemical aspects. *J Psychiatr Res* 11: 13–23.

Arias, H., Santamaria, A. and Ali, S. (2009) Pharmacological and neurotoxicological actions mediated by bupropion and diethylpropion. *Int Rev Neurobiol* 88: 223–255.

Barak, S. (2009) Modeling cholinergic aspects of schizophrenia: focus on the antimuscarinic syndrome. *Behav Brain Res* 204: 335–351.

Barak, S. and Weiner, I. (2011) Putative cognitive enhancers in preclinical models related to schizophrenia: the search for an elusive target. *Pharmacol Biochem Behav* 99: 164–189.

Behrens, M., Ali, S., Dao, D., Lucero, J., Shekhtman, G., Quick, K. *et al.* (2007) Ketamine-induced loss of phenotype of fast-spiking interneurons is mediated by NADPH-oxidase. *Science* 318: 1645–1647.

Bell, D. (1973) The experimental reproduction of amphetamine psychosis. *Arch Gen Psychiatry* 29: 35–40.

Boonstra, G., Burger, H., Grobbee, D. and Kahn, R. (2011) Antipsychotic prophylaxis is needed after remission from a first psychotic episode in schizophrenia patients: results from an aborted randomised trial. *Int J Psychiatry Clin Pract* 15: 128–134.

Bramness, J., Gundersen, O., Guterstam, J., Rognli, E., Konstenius, M., Loberg, E. *et al.* (2012) Amphetamine-induced psychosis - a separate diagnostic entity or primary psychosis triggered in the vulnerable? *BMC Psychiatry* 12: 221–244.

Breakey, W., Goodell, H., Lorenz, P. and McHugh, P. (1974) Hallucinogenic drugs as precipitants of schizophrenia. *Psychol Med* 4: 255–261.

Breese, G., Knapp, D. and Moy, S. (2002) Integrative role for serotonergic and glutamatergic receptor mechanisms in the action of NMDA antagonists: potential relationships to antipsychotic drug actions on NMDA antagonist responsiveness. *Neurosci Biobehav Rev* 26: 441–455.

Buchanan, R., Keefe, R., Lieberman, J., Barch, D., Csernansky, J., Goff, D. *et al.* (2011) A randomized clinical trial of MK-0777 for the treatment of cognitive impairments in people with schizophrenia. *Biol Psychiatry* 69: 442–449.

Carhart-Harris, R., Brugger, S., Nutt, D. and Stone, J. (2013a) Psychiatry's next top model: cause for a re-think on drug models of psychosis and other psychiatric disorders. *J Psychopharmacol* 27: 771–778.

Carhart-Harris, R., Erritzoe, D., Williams, T., Stone, J., Reed, L., Colasanti, A. *et al.* (2012) Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin. *Proc Natl Acad Sci U S A* 109: 2138–2143.

Carhart-Harris, R., Leech, R., Erritzoe, D., Williams, T., Stone, J., Evans, J. *et al.* (2013b) Functional connectivity measures after psilocybin inform a novel hypothesis of early psychosis. *Schizophr Bull* 39: 1343–1351.

Carter, O., Burr, D., Pettigrew, J., Wallis, G., Hasler, F. and Vollenweider, F. (2005) Using psilocybin to investigate the relationship between attention, working memory, and the serotonin 1A and 2A receptors. *J Cogn Neurosci* 17: 1497–1508.

Cerimele, J. and Durango, A. (2012) Does varenicline worsen psychiatric symptoms in patients with schizophrenia or schizoaffective disorder? A review of published studies. *J Clin Psychiatry* 73: e1039–e1047.

Corlett, P., Frith, C. and Fletcher, P. (2009) From drugs to deprivation: a Bayesian framework for understanding models of psychosis. *Psychopharmacology (Berl)* 206: 515–530.

Corlett, P., Honey, G. and Fletcher, P. (2007) From prediction error to psychosis: ketamine as a pharmacological model of delusions. *J Psychopharmacol* 21: 238–252.

Curran, H., D'Souza, D., Robbins, T. and Fletcher, P. (2009) Modelling psychosis. *Psychopharmacology (Berl)* 206: 513–514.

Davis, K., Kahn, R., Ko, G. and Davidson, M. (1991) Dopamine in schizophrenia: a review and reconceptualization. *Am J Psychiatry* 148: 1474–1486.

de Paulis, T. (2001) M-100907 (Aventis). *Curr Opin Investig Drugs* 2: 123–132.

Deakin, J., Lees, J., McKie, S., Hallak, J., Williams, S. and Dursun, S. (2008) Glutamate and the neural basis of the subjective effects of ketamine: a pharmaco-magnetic resonance imaging study. *Arch Gen Psychiatry* 65: 154–164.

Del Arco, A., Martinez, R. and Mora, F. (1998) Amphetamine increases extracellular concentrations of glutamate in the prefrontal cortex of the awake rat: a microdialysis study. *Neurochem Res* 23: 1153–1158.

Demjaha, A., Egerton, A., Murray, R., Kapur, S., Howes, O., Stone, J. *et al.* (2014) Antipsychotic treatment resistance in schizophrenia associated with elevated glutamate levels but normal dopamine function. *Biol Psychiatry* 75(5): e11–e13.

Demjaha, A., Murray, R., McGuire, P., Kapur, S. and Howes, O. (2012) Dopamine synthesis capacity in patients with treatment-resistant schizophrenia. *Am J Psychiatry* 169: 1203–1210.

Deutsch, S., Rosse, R., Schwartz, B. and Mastropaolo, J. (2001) A revised excitotoxic hypothesis of schizophrenia: therapeutic implications. *Clin Neuropharmacol* 24: 43–49.

Domino, E., Mirzoyan, D. and Tsukada, H. (2004) N-methyl-D-aspartate antagonists as drug models of schizophrenia: a surprising link to tobacco smoking. *Prog Neuropsychopharmacol Biol Psychiatry* 28: 801–811.

Driesen, N., McCarthy, G., Bhagwagar, Z., Bloch, M., Calhoun, V., D'Souza, D. *et al.* (2013) Relationship of resting brain hyperconnectivity and schizophrenia-like symptoms produced by the NMDA receptor antagonist ketamine in humans. *Mol Psychiatry* 18: 1199–1204.

D'Souza, D. (2007) Cannabinoids and psychosis. *Int Rev Neurobiol* 78: 289–326.

D'Souza, D., Abi-Saab, W., Madonick, S., Forselius-Bielen, K., Doersch, A., Braley, G. *et al.* (2005) Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. *Biol Psychiatry* 57: 594–608.

D'Souza, D.C., Ahn, K., Bhakta, S., Elander, J., Singh, N., Nadim, H. *et al.* (2012) Nicotine fails to attenuate ketamine-induced cognitive deficits and negative and positive symptoms in humans: implications for schizophrenia. *Biol Psychiatry* 72: 785–794.

D'Souza, D., Gil, R., Zuzarte, E., MacDougall, L., Donahue, L., Ebersole, J. *et al.* (2006) Gamma-aminobutyric acid-serotonin interactions in healthy men: implications for network models of psychosis and dissociation. *Biol Psychiatry* 59: 128–137.

D'Souza, D., Perry, E., MacDougall, L., Ammerman, Y., Cooper, T., Wu, Y. *et al.* (2004) The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology* 29: 1558–1572.

Ebdrup, B., Rasmussen, H., Arnt, J. and Glenthoj, B. (2011) Serotonin 2A receptor antagonists for treatment of schizophrenia. *Expert Opin Investig Drugs* 20: 1211–1223.

Egerton, A., Brugger, S., Raffin, M., Barker, G., Lythgoe, D., McGuire, P. *et al.* (2012) Anterior cingulate glutamate levels related to clinical status following treatment in first-episode schizophrenia *Neuropsychopharmacology* 37: 2515–2521.

Farren, C., Hameedi, F., Rosen, M., Woods, S., Jatlow, P. and Kosten, T. (2000) Significant interaction between clozapine and cocaine in cocaine addicts. *Drug Alcohol Depend* 59: 153–163.

Featherstone, R., Kapur, S. and Fletcher, P. (2007) The amphetamine-induced sensitized state as a model of schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 31: 1556–1571.

Fernandez-Espejo, E., Viveros, M., Nunez, L., Ellenbroek, B. and Rodriguez de Fonseca, F. (2009) Role of cannabis and endocannabinoids in the genesis of schizophrenia. *Psychopharmacology (Berl)* 206: 531–549.

Fletcher, P. and Honey, G. (2006) Schizophrenia, ketamine and cannabis: evidence of overlapping memory deficits. *Trends Cogn Sci* 10: 167–174.

Fletcher, P., Tenn, C., Rizos, Z., Lovic, V. and Kapur, S. (2005) Sensitization to amphetamine, but not PCP, impairs attentional set shifting: reversal by a D1 receptor agonist injected into the medial prefrontal cortex. *Psychopharmacology (Berl)* 183: 190–200.

Ford, J., Mathalon, D., Whitfield, S., Faustman, W. and Roth, W. (2002) Reduced communication between frontal and temporal lobes during talking in schizophrenia *Biol Psychiatry* 51: 485–492.

Ford, J., Roach, B., Faustman, W. and Mathalon, D. (2007) Synch before you speak: auditory hallucinations in schizophrenia. *Am J Psychiatry* 164: 458–66.

Foster, D., Jones, C. and Conn, P. (2012) Emerging approaches for treatment of schizophrenia: modulation of cholinergic signaling. *Discov Med* 14: 413–420.

Freedman, R., Olincy, A., Buchanan, R., Harris, J., Gold, J., Johnson, L. *et al.* (2008) Initial phase 2 trial of a nicotinic agonist in schizophrenia. *Am J Psychiatry* 165: 1040–1047.

Gallinat, J., Rentzsch, J. and Roser, P. (2012) Neurophysiological effects of cannabinoids: implications for psychosis research. *Curr Pharm Des* 18: 4938–4949.

Geyer, M. and Vollenweider, F. (2008) Serotonin research: contributions to understanding psychoses. *Trends Pharmacol Sci* 29: 445–453.

Gill, K., Lodge, D., Cook, J., Aras, S. and Grace, A. (2011) A novel alpha5GABA(A)R-positive allosteric modulator reverses hyperactivation of the dopamine system in the MAM model of schizophrenia. *Neuropsychopharmacology* 36: 1903–1911.

Goff, D. and Coyle, J. (2001) The emerging role of glutamate in the pathophysiology and treatment of schizophrenia. *Am J Psychiatry* 158: 1367–1377.

Hallak, J., Dursun, S., Bosi, D., de Macedo, L., Machado-de-Sousa, J., Abrao, J. *et al.* (2011) The interplay of cannabinoid and NMDA glutamate receptor systems in humans: preliminary evidence of interactive effects of cannabidiol and ketamine in healthy human subjects *Prog Neuropsychopharmacol Biol Psychiatry* 35: 198–202.

Harris, D. and Batki, S. (2000) Stimulant psychosis: symptom profile and acute clinical course. *Am J Addict* 9: 28–37.

Hertzmann, M., Reba, R. and Kotlyarov, E. (1990) Single photon emission computed tomography in phencyclidine and related drug abuse. *Am J Psychiatry* 147: 255–256.

Homayoun, H. and Moghaddam, B. (2007) NMDA receptor hypofunction produces opposite effects on prefrontal cortex interneurons and pyramidal neurons *J Neurosci* 27: 11496–11500.

Howes, O., Kambeitz, J., Kim, E., Stahl, D., Slifstein, M., Abi-Dargham, A. *et al.* (2012) The nature of dopamine dysfunction in schizophrenia and what this means for treatment. *Arch Gen Psychiatry* 69: 776–786.

Hyde, C., Glancy, G., Omerod, P., Hall, D. and Taylor, G. (1978) Abuse of indigenous psilocybin mushrooms: a new fashion and some psychiatric complications. *Br J Psychiatry* 132: 602–604.

Japha, K. and Koch, M. (1999) Picrotoxin in the medial prefrontal cortex impairs sensorimotor gating in rats: reversal by haloperidol. *Psychopharmacology (Berl)* 144: 347–354.

Javitt, D. (1987) Negative schizophrenic symptomatology and the PCP (phencyclidine) model of schizophrenia. *Hillside J Clin Psychiatry* 9: 12–35.

Javitt, D. and Zukin, S. (1991) Recent advances in the phencyclidine model of schizophrenia. *Am J Psychiatry* 148: 1301–1308.

Jentsch, J., Redmond, D., Jr, Elsworth, J., Taylor, J., Youngren, K. and Roth, R. (1997) Enduring cognitive deficits and cortical dopamine dysfunction in monkeys after long-term administration of phencyclidine. *Science* 277: 953–955.

Jentsch, J. and Roth, R. (1999) The neuropsychopharmacology of phencyclidine: from NMDA receptor hypofunction to the dopamine hypothesis of schizophrenia. *Neuropsychopharmacology* 20: 201–225.

Johnson, M., MacLean, K., Reissig, C., Prisinzano, T. and Griffiths, R. (2011) Human psychopharmacology and dose-effects of salvinorin A, a kappa opioid agonist hallucinogen present in the plant salvia divinorum. *Drug Alcohol Depend* 115: 150–155.

Jones, C., Watson, D. and Fone, K. (2011) Animal models of schizophrenia. *Br J Pharmacol* 164: 1162–1194.

Kapur, S. and Mamo, D. (2003) Half a century of antipsychotics and still a central role for dopamine D2 receptors *Prog Neuropsychopharmacol Biol Psychiatry* 27: 1081–1090.

Kapur, S., Mizrahi, R. and Li, M. (2005) From dopamine to salience to psychosis - linking biology, pharmacology and phenomenology of psychosis. *Schizophr Res* 79: 59–68.

Kapur, S. and Seeman, P. (2002) NMDA receptor antagonists ketamine and PCP have direct effects on the dopamine D(2) and serotonin 5-HT(2) receptors-implications for models of schizophrenia. *Mol Psychiatry* 7: 837–44.

Kegeles, L., Abi-Dargham, A., Frankle, W., Gil, R., Cooper, T., Slifstein, M. *et al.* (2010) Increased synaptic dopamine function in associative regions of the striatum in schizophrenia *Arch Gen Psychiatry* 67: 231–239.

Kegeles, L., Martinez, D., Kochan, L., Hwang, D., Huang, Y., Mawlawi, O. *et al.* (2002) NMDA antagonist effects on striatal dopamine release: positron emission tomography studies in humans. *Synapse* 43: 19–29.

Klinkenberg, I. and Blokland, A. (2010) The validity of scopolamine as a pharmacological model for cognitive impairment: a review of animal behavioral studies. *Neurosci Biobehav Rev* 34: 1307–1350.

Klosterkotter, J., Hellmich, M., Steinmeyer, E. and Schultze-Lutter, F. (2001) Diagnosing schizophrenia in the initial prodromal phase. *Arch Gen Psychiatry* 58: 158–164.

Koethe, D., Gerth, C., Neatby, M., Haensel, A., Thies, M., Schneider, U. *et al.* (2006) Disturbances of visual information processing in early states of psychosis and experimental delta-9-tetrahydrocannabinol altered states of consciousness. *Schizophr Res* 88: 142–150.

Koethe, D., Hoyer, C. and Leweke, F. (2009) The endocannabinoid system as a target for modelling psychosis. *Psychopharmacology (Berl)* 206: 551–561.

Krystal, J., Karper, L., Seibyl, J., Freeman, G., Delaney, R., Bremner, J. *et al.* (1994) Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry* 51: 199–214.

Krystal, J., Perry, E., J., Gueorguieva, R., Belger, A., Madonick, S., Abi-Dargham, A.

et al. (2005) Comparative and interactive human psychopharmacologic effects of ketamine and amphetamine: implications for glutamatergic and dopaminergic model psychoses and cognitive function. *Arch Gen Psychiatry* 62: 985–994.

Kuepper, R., Morrison, P., van Os, J., Murray, R., Kenis, G. and Henquet, C. (2010) Does dopamine mediate the psychosis-inducing effects of cannabis? A review and integration of findings across disciplines. *Schizophr Res* 121: 107–117.

Kumar, S., Kodela, S., Detweiler, J., Kim, K. and Detweiler, M. (2011) Bupropion-induced psychosis: folklore or a fact? A systematic review of the literature. *Gen Hosp Psychiatry* 33: 612–617.

Lahti, A., Holcomb, H., Medoff, D. and Tamminga, C. (1995a) Ketamine activates psychosis and alters limbic blood flow in schizophrenia. *Neuroreport* 6: 869–872.

Lahti, A., Koffel, B., LaPorte, D. and Tamminga, C. (1995b) Subanesthetic doses of ketamine stimulate psychosis in schizophrenia. *Neuropsychopharmacology* 13: 9–19.

Lange, J., Daniel, J., Homer, K., Reed, M. and Clapp, J. (2010) Salvia divinorum: effects and use among YouTube users. *Drug Alcohol Depend* 108: 138–140.

Langer, O. and Halldin, C. (2002) PET and SPET tracers for mapping the cardiac nervous system. *Eur J Nucl Med Mol Imaging* 29: 416–434.

Laruelle, M., Abi-Dargham, A., van Dyck, C., Gil, R., D'Souza, C., Erdos, J. *et al.* (1996) Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects. *Proc Natl Acad Sci U S A* 93: 9235–9240.

Laruelle, M., Abi-Dargham, A., van Dyck, C., Gil, R., D'Souza, D., Krystal, J. *et al.* (2000) Dopamine and serotonin transporters in patients with schizophrenia: an imaging study with [(123)I]beta-CIT. *Biol Psychiatry* 47: 371–379

Laruelle, M., Kegeles, L. and Abi-Dargham, A. (2003) Glutamate, dopamine, and schizophrenia: from pathophysiology to treatment. *Ann NY Acad Sci* 1003: 138–158.

Law, A. and Deakin, J. (2001) Asymmetrical reductions of hippocampal NMDAR1 glutamate receptor mRNA in the psychoses. *Neuroreport* 12: 2971–2974.

Levin, E., Petro, A. and Caldwell, D. (2005) Nicotine and clozapine actions on pre-pulse inhibition deficits caused by N-methyl-D-aspartate (NMDA) glutamatergic receptor blockade. *Prog Neuropsychopharmacol Biol Psychiatry* 29: 581–586.

Levkovitz, Y., Levi, U., Braw, Y. and Cohen, H. (2007) Minocycline, a second-generation tetracycline, as a neuroprotective agent in an animal model of schizophrenia. *Brain Res* 1154: 154–162.

Leweke, F., Piomelli, D., Pahlisch, F., Muhl, D., Gerth, C., Hoyer, C. *et al.* (2012) Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Transl Psychiatry* 2: e94.

Lewis, D., Pierri, J., Volk, D., Melchitzky, D. and Woo, T. (1999) Altered GABA neurotransmission and prefrontal cortical dysfunction in schizophrenia. *Biol Psychiatry* 46: 616–626.

Liao, Y., Tang, J., Corlett, P., Wang, X., Yang, M., Chen, H. *et al.* (2011) Reduced dorsal prefrontal gray matter after chronic ketamine use. *Biol Psychiatry* 69: 42–48.

Lieberman, J., Dunbar, G., Segreti, A., Girgis, R., Seoane, F., Beaver, J. *et al.* (2013) A randomized exploratory trial of an alpha-7 nicotinic receptor agonist (TC-5619) for cognitive enhancement in schizophrenia. *Neuropsychopharmacology* 38: 968–975.

Lieberman, J., Stroup, T., McEvoy, J., Swartz, M., Rosenheck, R., Perkins, D. *et al.* (2005) Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 353: 1209–1223.

Linn, G., O'Keeffe, R., Schroeder, C., Lifshitz, K. and Javitt, D. (1999) Behavioral effects of chronic phencyclidine in monkeys. *Neuroreport* 10: 2789–2793.

Lodge, D. and Grace, A. (2011) Hippocampal dysregulation of dopamine system function and the pathophysiology of schizophrenia. *Trends Pharmacol Sci* 32: 507–513.

MacLean, K., Johnson, M., Reissig, C., Prisinzano, T. and Griffiths, R. (2013) Dose-related effects of salvinorin A in humans: dissociative, hallucinogenic, and memory effects. *Psychopharmacology (Berl)* 226: 381–392.

Malhotra, A., Pinals, D., Adler, C., Elman, I., Clifton, A., Pickar, D. *et al.* (1997) Ketamine-induced exacerbation of psychotic symptoms and cognitive impairment in neuroleptic-free schizophrenics. *Neuropsychopharmacology* 17: 141–150.

Marcotte, E., Pearson, D. and Srivastava, L. (2001) Animal models of schizophrenia: a critical review. *J Psychiatry Neurosci* 26: 395–410.

Marona-Lewicka, D., Nichols, C. and Nichols, D. (2011) An animal model of schizophrenia based on chronic LSD administration: old idea, new results. *Neuropharmacology* 61: 503–512.

Marsman, A., van den Heuvel, M., Klomp, D., Kahn, R., Luijten, P. and Hulshoff Pol, H. (2013) Glutamate in schizophrenia: a focused review and meta-analysis of (1)H-MRS studies. *Schizophr Bull* 39: 120–129.

Meldrum, B. (1982) GABA and acute psychoses. *Psychol Med* 12: 1–5.

Meltzer, H. (1996) Pre-clinical pharmacology of atypical antipsychotic drugs: a selective review. *Br J Psychiatry Suppl* 29: 23–31.

Meltzer, H. (1997) Treatment-resistant schizophrenia - the role of clozapine. *Curr Med Res Opin* 14: 1–20.

Mihalak, K., Carroll, F. and Luetje, C. (2006) Varenicline is a partial agonist at alpha4beta2 and a full agonist at alpha7 neuronal nicotinic receptors. *Mol Pharmacol* 70: 801–805.

Minzenberg, M., Poole, J., Benton, C. and Vinogradov, S. (2004) Association of anticholinergic load with impairment of complex attention and memory in schizophrenia. *Am J Psychiatry* 161: 116–124.

Mirza, N., Peters, D. and Sparks, R. (2003) Xanomeline and the antipsychotic potential of muscarinic receptor subtype selective agonists. *CNS Drug Rev* 9: 159–186.

Moghaddam, B., Adams, B., Verma, A. and Daly, D. (1997) Activation of glutamatergic neurotransmission by ketamine: a novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. *J Neurosci* 17: 2921–2927.

Monte, A., de Souza, G., McIntyre, R., Soczynska, J., dos Santos, J., Cordeiro, R. *et al.* (2013) Prevention and reversal of ketamine-induced schizophrenia related behavior by minocycline in mice: Possible involvement of antioxidant and nitrergic pathways. *J Psychopharmacol* 27: 1032–1043.

Morgan, C., Mofeez, A., Brandner, B., Bromley, L. and Curran, H. (2004) Acute effects of ketamine on memory systems and psychotic symptoms in healthy volunteers. *Neuropsychopharmacology* 29: 208–218.

Morrison, P., Nottage, J., Stone, J., Bhattacharyya, S., Tunstall, N., Brenneisen, R. *et al.* (2011) Disruption of frontal theta coherence by Delta(9)-tetrahydrocannabinol is associated with positive psychotic symptoms *Neuropsychopharmacology* 36: 827–836.

Morrison, P. and Stone, J. (2011) Synthetic delta-9-tetrahydrocannabinol elicits schizophrenia-like negative symptoms which are distinct from sedation. *Clin Psychopharm Clin* 26: 77–80.

Morrison, P., Zois, V., McKeown, D., Lee, T., Holt, D., Powell, J. *et al.* (2009) The acute effects of synthetic intravenous Delta9-tetrahydrocannabinol on psychosis, mood and cognitive functioning *Psychol Med* 39: 1607–1616.

Mosolov, S., Potapov, A. and Ushakov, U. (2012) Remission in schizophrenia: results of cross-sectional with 6-month follow-up period and 1-year observational therapeutic studies in an outpatient population. *Ann Gen Psychiatry* 11: 1-859X-11-1.

Muschamp, J., Regina, M., Hull, E., Winter, J. and Rabin, R. (2004) Lysergic acid diethylamide and [-]-2,5-dimethoxy-4-methylamphetamine increase extracellular glutamate in rat prefrontal cortex. *Brain Res* 1023: 134–140.

Narendran, R., Frankle, W., Keefe, R., Gil, R., Martinez, D., Slifstein, M. *et al.* (2005) Altered prefrontal dopaminergic function in chronic recreational ketamine users. *Am J Psychiatry* 162: 2352–2359.

Neill, J., Barnes, S., Cook, S., Grayson, B., Idris, N., McLean, S. *et al.* (2010) Animal models of cognitive dysfunction and negative symptoms of schizophrenia: focus on NMDA receptor antagonism. *Pharmacol Ther* 128: 419–432.

Okugawa, G., Tamagaki, C. and Agartz, I. (2007) Frontal and temporal volume size of grey and white matter in patients with schizophrenia: an MRI parcellation study. *Eur Arch Psychiatry Clin Neurosci* 257: 304–307.

Olney, J. and Farber, N. (1995) Glutamate receptor dysfunction and schizophrenia. *Arch Gen Psychiatry* 52: 998–1007.

Perry, E. and Perry, R. (1995) Acetylcholine and hallucinations: disease-related compared to drug-induced alterations in human consciousness. *Brain Cogn* 28: 240–258.

Pilowsky, L., Bressan, R., Stone, J., Erlandsson, K., Mulligan, R., Krystal, J. *et al.* (2006) First in vivo evidence of an NMDA receptor deficit in medication-free schizophrenic patients. *Mol Psychiatry* 11: 118–119.

Pistis, M., Ferraro, L., Pira, L., Flore, G., Tanganelli, S., Gessa, G. *et al.* (2002) Delta(9)-tetrahydrocannabinol decreases extracellular GABA and increases extracellular glutamate and dopamine levels in the rat prefrontal cortex: an in vivo microdialysis study. *Brain Res* 948: 155–158.

Pratt, J., Winchester, C., Dawson, N. and Morris, B. (2012) Advancing schizophrenia drug discovery: optimizing rodent models to bridge the translational gap. *Nat Rev Drug Discov* 11: 560–579.

Przekop, P. and Lee, T. (2009) Persistent psychosis associated with salvia divinorum use. *Am J Psychiatry* 166: 832.

Quednow, B., Kometer, M., Geyer, M. and Vollenweider, F. (2012) Psilocybin-induced deficits in automatic and controlled inhibition are attenuated by ketanserin in healthy human volunteers. *Neuropsychopharmacology* 37: 630–640.

Raedler, T. (2007) Comparison of the in-vivo muscarinic cholinergic receptor availability in patients treated with clozapine and olanzapine. *Int J Neuropsychopharmacol* 10: 275–80.

Raedler, T., Knable, M., Jones, D., Urbina, R., Gorey, J., Lee, K. *et al.* (2003) In vivo determination of muscarinic acetylcholine receptor availability in schizophrenia. *Am J Psychiatry* 160: 118–127.

Ramadan, S., Lin, A. and Stanwell, P. (2013) Glutamate and glutamine: a review of in vivo MRS in the human brain. *NMR Biomed* 26: 1630–1646.

Ranganathan, M., Schnakenberg, A., Skosnik, P., Cohen, B., Pittman, B., Sewell, R. *et al.* (2012) Dose-related behavioral, subjective, endocrine, and psychophysiological effects of the kappa opioid agonist Salvinorin A in humans. *Biol Psychiatry* 72: 871–879.

Realini, N., Rubino, T. and Parolaro, D. (2009) Neurobiological alterations at adult age triggered by adolescent exposure to cannabinoids. *Pharmacol Res* 60: 132–138.

Richtand, N., Woods, S., Berger, S. and Strakowski, S. (2001) D3 dopamine receptor, behavioral sensitization, and psychosis. *Neurosci Biobehav Rev* 25: 427–443.

Ripoll, N., Bronnec, M. and Bourin, M. (2004) Nicotinic receptors and schizophrenia. *Curr Med Res Opin* 20: 1057–1074.

Rotaru, D., Lewis, D. and Gonzalez-Burgos, G. (2012) The role of glutamatergic inputs onto parvalbumin-positive interneurons: relevance for schizophrenia. *Rev Neurosci* 23: 97–109.

Roth, B., Hanizavareh, S. and Blum, A. (2004) Serotonin receptors represent highly favorable molecular targets for cognitive enhancement in schizophrenia and other disorders. *Psychopharmacology (Berl)* 174: 17–24.

Rothman, D., De Feyter, H., de Graaf, R., Mason, G. and Behar, K. (2011) 13C MRS studies of neuroenergetics and neurotransmitter cycling in humans. *NMR Biomed* 24: 943–957.

Rowland, L., Bustillo, J., Mullins, P., Jung, R., Lenroot, R., Landgraf, E. *et al.* (2005) Effects of ketamine on anterior cingulate glutamate metabolism in healthy humans: a 4-T proton MRS study. *Am J Psychiatry* 162: 394–396.

Rubino, T., Vigano', D., Realini, N., Guidali, C., Braida, D., Capurro, V. *et al.* (2008) Chronic delta 9-tetrahydrocannabinol during adolescence provokes sex-dependent changes in the emotional profile in adult rats: behavioral and biochemical correlates. *Neuropsychopharmacology* 33: 2760–2771.

Rudolph, U. and Knoflach, F. (2011) Beyond classical benzodiazepines: novel therapeutic potential of GABAA receptor subtypes. *Nat Rev Drug Discov* 10: 685–697.

Schneider, M. and Koch, M. (2003) Chronic pubertal, but not adult chronic cannabinoid treatment impairs sensorimotor gating, recognition memory, and the performance in a progressive ratio task in adult rats. *Neuropsychopharmacology* 28: 1760–1769.

Schwartz, T., Sachdeva, S. and Stahl, S. (2012) Glutamate neurocircuitry: theoretical underpinnings in schizophrenia. *Front Pharmacol* 3: 195.

Scruggs, J., Schmidt, D. and Deutch, A. (2003) The hallucinogen 1-[2,5-dimethoxy-4-iodophenyl]-2-aminopropane (DOI) increases cortical extracellular glutamate levels in rats. *Neurosci Lett* 346: 137–140.

Seeman, P. (1987) Dopamine receptors and the dopamine hypothesis of schizophrenia. *Synapse* 1: 133–152.

Seeman, P. and Kapur, S. (2000) Schizophrenia: more dopamine, more D2 receptors. *Proc Natl Acad Sci U S A* 97: 7673–7675.

Seeman, P. and Lee, T. (1975) Antipsychotic drugs: direct correlation between clinical potency and presynaptic action on dopamine neurons. *Science* 188: 1217–1219.

Segal, D. and Mandell, A. (1974) Long-term administration of d-amphetamine: progressive augmentation of motor activity and stereotypy. *Pharmacol Biochem Behav* 2: 249–255.

Shekhar, A., Potter, W., Lightfoot, J., Lienemann, J., Dube, S., Mallinckrodt, C. *et al.* (2008) Selective muscarinic receptor agonist xanomeline as a novel treatment approach for schizophrenia. *Amer J Psychiatry* 165: 1033–1039.

Solowij, N. and Michie, P. (2007) Cannabis and cognitive dysfunction: parallels with endophenotypes of schizophrenia? *J Psychiatry Neurosci* 32: 30–52.

Sorce, S., Schiavone, S., Tucci, P., Colaianna, M., Jaquet, V., Cuomo, V. *et al.* (2010) The NADPH oxidase NOX2 controls glutamate release: a novel mechanism involved in psychosis-like ketamine responses. *J Neurosci* 30: 11317–11325.

Steen, R., Mull, C., McClure, R., Hamer, R. and Lieberman, J. (2006) Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies. *Br J Psychiatry* 188: 510–518.

Stefani, M. and Moghaddam, B. (2005) Transient N-methyl-D-aspartate receptor blockade in early development causes lasting cognitive deficits relevant to schizophrenia. *Biol Psychiatry* 57: 433–436.

Stefansson, H., Rujescu, D., Cichon, S., Pietilainen, O., Ingason, A., Steinberg, S. *et al.* (2008) Large recurrent microdeletions associated with schizophrenia. *Nature* 455: 232–236.

Steinpreis, R., Sokolowski, J., Papanikolaou, A. and Salamone, J. (1994) The effects of haloperidol and clozapine on PCP- and amphetamine-induced suppression of social behavior in the rat. *Pharmacol Biochem Behav* 47: 579–585.

Stone, J., Dietrich, C., Edden, R., Mehta, M., De Simoni, S., Reed, L. *et al.* (2012a) Ketamine effects on brain GABA and glutamate levels with 1H-MRS: relationship to ketamine-induced psychopathology. *Mol Psychiatry* 17: 664–665.

Stone, J., Erlandsson, K., Arstad, E., Squassante, L., Teneggi, V., Bressan, R. *et al.* (2008) Relationship between ketamine-induced psychotic symptoms and NMDA receptor occupancy: a [(123)I]CNS-1261 SPET study. *Psychopharmacology* 197: 401–408.

Stone, J., Fisher, H., Major, B., Chisholm, B., Woolley, J., Lawrence, J. *et al.* (2014a) Cannabis use and first-episode psychosis: relationship with manic and psychotic symptoms, and with age at presentation. *Psychol Med* 44: 499–506.

Stone, J., Morrison, P., Brugger, S., Nottage, J., Bhattacharyya, S., Sumich, A. *et al.* (2012b) Communication breakdown: delta-9 tetrahydrocannabinol effects on pre-speech neural coherence. *Mol Psychiatry* 17: 568–569.

Stone, J., Pepper, F., Fam, J., Furby, H., Hughes, E., Morgan, C. *et al.* (2014b) Glutamate, N-acetyl aspartate and psychotic symptoms in chronic ketamine users. *Psychopharmacology (Berl)* 2431: 2107–2116.

Stone, J., Raffin, M., Morrison, P. and McGuire, P. (2010) Review: The biological basis of antipsychotic response in schizophrenia *J Psychopharmacol* 24: 953–964.

Strassman, R., Qualls, C., Uhlenhuth, E. and Kellner, R. (1994) Dose-response study of N,N-dimethyltryptamine in humans. II. Subjective effects and preliminary results of a new rating scale. *Arch Gen Psychiatry* 51: 98–108.

Szulc, A., Konarzewska, B., Galinska-Skok, B., Lazarczyk, J., Waszkiewicz, N., Tarasow, E. *et al.* (2013) Proton magnetic resonance spectroscopy measures related to short-term symptomatic outcome in chronic schizophrenia. *Neurosci Lett* 547: 37–41.

Tejeda, H., Shippenberg, T. and Henriksson, R. (2012) The dynorphin/kappa-opioid receptor system and its role in psychiatric disorders. *Cell Mol Life Sci* 69: 857–896.

Tenn, C., Fletcher, P. and Kapur, S. (2003) Amphetamine-sensitized animals show a sensorimotor gating and neurochemical abnormality similar to that of schizophrenia. *Schizophr Res* 64: 103–114.

Thomas, A., Baillie, G., Phillips, A., Razdan, R., Ross, R. and Pertwee, R. (2007) Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro. *Br J Pharmacol* 150: 613–623.

Tsai, G. and Coyle, J. (2002) Glutamatergic mechanisms in schizophrenia. *Annu Rev Pharmacol Toxicol* 42: 165–179.

Uehara, T., Sumiyoshi, T., Seo, T., Matsuoka, T., Itoh, H., Suzuki, M. *et al.* (2010) Neonatal exposure to MK-801, an N-methyl-D-aspartate receptor antagonist, enhances methamphetamine-induced locomotion and disrupts sensorimotor gating in pre- and postpubertal rats. *Brain Res* 1352: 223–230.

Ujike, H. (2002) Stimulant-induced psychosis and schizophrenia: the role of sensitization. *Curr Psychiatry Rep* 4: 177–184.

Vardy, M. and Kay, S. (1983) LSD psychosis or LSD-induced schizophrenia? A multimethod inquiry. *Arch Gen Psychiatry* 40: 877–883.

Verrico, C., Liu, S., Bitler, E., Gu, H., Sampson, A., Bradberry, C. *et al.* (2012) Delay- and dose-dependent effects of Delta(9)-tetrahydrocannabinol administration on spatial and object working memory tasks in adolescent rhesus monkeys. *Neuropsychopharmacology* 37: 1357–1366.

Vollenweider, F. and Geyer, M. (2001) A systems model of altered consciousness: integrating natural and drug-induced psychoses. *Brain Res Bull* 56: 495–507.

Wang, C. and Johnson, K. (2005) Differential effects of acute and subchronic administration on phencyclidine-induced neurodegeneration in the perinatal rat. *J Neurosci Res* 81: 284–292.

Wang, M., Pei, L., Fletcher, P., Kapur, S., Seeman, P. and Liu, F. (2010) Schizophrenia, amphetamine-induced sensitized state and acute amphetamine exposure all show a common alteration: increased dopamine D2 receptor dimerization. *Mol Brain* 3: 25-6606-3-25.

Williams, J., McGuffin, P., Nothen, M. and Owen, M. (1997) Meta-analysis of association between the 5-HT2a receptor T102C polymorphism and schizophrenia. EMASS Collaborative Group. European Multicentre Association Study of Schizophrenia. *Lancet* 349: 1221.

Wolkin, A., Sanfilipo, M., Angrist, B., Duncan, E., Wieland, S., Wolf, A. *et al.* (1994) Acute d-amphetamine challenge in schizophrenia: effects on cerebral glucose utilization and clinical symptomatology. *Biol Psychiatry* 36: 317–325.

Yamamoto, S., Yoshimura, M., Shin, M., Wakita, M., Nonaka, K. and Akaike, N. (2011) GABA(A) receptor-mediated presynaptic inhibition on glutamatergic transmission. *Brain Res Bull* 84: 22–30.

Zhang, L., Shirayama, Y., Iyo, M. and Hashimoto, K. (2007) Minocycline attenuates hyperlocomotion and prepulse inhibition deficits in mice after administration of the NMDA receptor antagonist dizocilpine *Neuropsychopharmacology* 32: 2004–2010.