The psychotomimetic effects of PCP, LSD and MDMA: Pharmacological models of schizophrenia?

Vibeke S. Catts[1], Stanley V. Catts[1,2]
[1]School of Medicine, The University of Queensland; [2]Mental Health Centre, Royal Brisbane and Women's Hospital

In this Review the potential role of glutamatergic and serotonergic neurotransmitter systems in the pathophysiology of schizophrenia is examined from the perspective of the psychotomimetic effects of 1) phencyclidine (PCP) and ketamine, non-competitive antagonists of the *N*-methyl-D-aspartate (NMDA) glutamatergic receptor that bind at the intra-channel site of the receptor to prevent calcium ion flux into the cell 2) D-lysergic acid diethylamide (LSD), a serotonin-like hallucinogenic indoleamine that acts as an agonist at the serotonin-subtype-2A (5HT2A) receptor, and 3) 3,4-methylenedioxy-methamphetamine (MDMA), an indirect serotonin agonist. These drugs, variously called hallucinogens, schizophrenomimetics, psychotogens or psychotomimetics, have in common reports that they can induce psychotic symptoms (hallucinations, delusions, formal thought disorder, or catatonia-like abnormalities) in the absence of delirium. The primary question addressed herein, whether PCP-induced psychosis is a valid model of schizophrenia, gives rise to additional questions about the validity of ketamine challenge at subanaesthetic doses in humans as a model of PCP psychosis, and in turn, questions about the validity of drug-induced changes in non-human animals (rodents, monkeys) treated with PCP and its analogues (ketamine or dizocilpine [MK-801]) as models of PCP-induced psychosis.

A model is defined as any experimental preparation developed for the purpose of studying a condition in the same or different species (1). In evaluating disease models the following criteria (2) apply:

- How similar phenomenologically is the behavioural performance of the model compared to the symptoms of the disease? (face validity)

- How closely does the model replicate the hypothesised pathophysiology or theoretical process underlying the disease? (construct validity)
- How accurately can predictions be made about the disease based on performance of the model? (predictive validity).

An extension of construct validity is aetiological validity, which refers to the degree of equivalence between the model-inducing manipulation and the aetiological factors causing the disease. Models must be reliable, in the sense that their performance can be accurately measured. Ideally, models also display discriminant validity (measures of the model's performance are un-correlated with those of models of other diseases) and convergent validity (multiple measures of the performance of the same model are highly correlated). Hence, the validity of a model relies as much on aetiological validity (how the model is induced or created) as on the validity of measures of its performance, which in turn depend on the validity of measures of the disease itself.

Modelling schizophrenia is difficult at all levels (2, 3). There are no agreed upon pathognomonic features; many of the symptoms are based on verbal report and cannot be measured in animals; the aetiology is multi-factorial and specific factors are unknown; the pathophysiology is ill-defined and may be heterogenous; and most disease measures applicable to *in vivo* animal models, e.g. deficits in working memory or prepulse inhibition (PPI), are not specific to schizophrenia. Rapid progress in therapeutics in other complex diseases (e.g. cancer) has been attributed to availability of valid animal and cellular models, and slow progress in schizophrenia attributed to the lack of these models (4). Some argue that drug development in schizophrenia has not progressed appreciably since the introduction of chlorpromazine (4-7). Others reason that only symptom reducing, and not disease modifying, treatments will arise when disease models for testing new drugs are based solely on symptom similarity and its behavioural measurement, as is the case with amphetamine-induced hyperlocomotion in rodents (e.g. 8, 9). These considerations imply that a useful disease model of schizophrenia will have more than face and construct validity by generating accurate predictions about the human pathophysiology and likely clinical effectiveness of novel pharmacotherapies. This

Review aims to assess the relative validity of NMDA antagonist models of schizophrenia compared with serotonergic models based on LSD- and MDMA-induced psychosis.

Human studies

For each drug of interest, this Section reviews the evidence for psychotomimetic effects in humans, in terms of induced transient symptoms with acute dosing, and the epidemiological association between formal psychotic disorder and chronic abuse. The phenomenological similarity of drug-induced symptoms and the clinical features of schizophrenia is closely examined. Where available, human neuroimaging and clinical biomarker studies are considered for comparison of drug-induced effects and deficits seen in schizophrenia. Ketamine is included in the review because most experimental evidence supporting the validity of the PCP model arose from studies using ketamine in humans. The literature on LSD and MDMA is briefly reviewed for comparative purposes.

Phencyclidine (PCP)

Phencyclidine [1-(1-phenylcyclohexyl)piperidine hydrochloride] was synthesized in 1956 (10). Preclinical testing indicated that PCP might be a safe intravenous (IV) anaesthetic because it induced analgesia and anaesthesia without circulatory or respiratory depression (10). PCP was tested as an anaesthetic in about 3000 patients in the late 1950's. The term 'dissociative anaesthetic' was coined because PCP induced a state of detachment, and dissociation from painful and environmental stimuli, without causing unconsciousness: during anaesthesia the patient remained immobile with fixed sightless staring, absent facial expression, and open mouth (11). PCP is highly lipid soluble and readily crosses the blood-brain barrier, inducing CNS effects within minutes of IV injection. The serum half-life of PCP was reported to vary between 4 to 72 hours (12, 13). When PCP was used as an IV anaesthetic, patients became responsive to auditory stimuli within 60 minutes (14) though orientation remained poor for up to 4 hours (15). Intravenous PCP induced dose-dependent effects: at doses of about 0.25 mg/kg (about 0.2 μM serum concentration), it produced complete insensibility to pain; at doses above 0.5 mg/kg (about 0.4 μM serum concentration), patients became delirious; and when doses were

increased towards 1 mg/kg (up to 0.8 μM serum concentration), severe rigidity, catatonia, and convulsions ensued (14, 16-18).

Early clinical use revealed that many patients experienced psychotic symptoms as they emerged from PCP anaesthesia (11, 14, 15, 19). Emergence phenomena included: agitation, bizarre behaviour, paranoia, formal thought disorder, hallucinations, and delusions, typically lasting for 12-72 hours but occasionally persisting for up to 10 days (14, 19). Symptoms were schizophrenia-like, especially the motor changes (15). Flat facies, fixed staring, manneristic grimacing, generalized rigidity, and plastic stiffness very similar to 'cerea flexibilitas' occurred. Stereotypic verbalizations of select phrases were uttered. PCP-induced agitation was associated with atypical movements: head rolling or shaking the head from side to side was common. Attempts to prevent emergence reactions by pre-treatment with haloperidol or diazepam were relatively unsuccessful: diazepam (20) appeared to be as effective as haloperidol (21). Phencyclidine was withdrawn from the market for human use in 1965. A veterinarian formulation was introduced in 1967 but because of a growing abuse problem all legal manufacture of the drug was ceased in 1979.

Despite its propensity to cause adverse reactions, PCP abuse became widespread. It was relatively inexpensive to manufacture and the starting materials, used in many industrial processes, were readily available (22). Illicit PCP use first appeared in 1965 on the West Coast of the USA (13). Initially the drug was ingested orally (called the 'PeaCe Pill'). Slow oral absorption resulted in inadvertent high dosing and frequent adverse reactions, limiting its appeal (22). Once street users discovered that the dose could be lowered and self-titrated by smoking PCP added to cigarettes, illicit use escalated. National surveys in the USA indicate that peak use of PCP occurred between 1977 and 1979 (23, 24). Between 1976 and 1977 the National Institute of Drug Abuse (NIDA) reported a doubling (from 3% to 5.8%) of the number of 12- to 17-year-old users of PCP, and a 50% increase (from 9.5% to 13.9%) in 18- to 25-year-old users (22). A survey of 319 adult users reported negative events on 100% of use occasions (25), including speech difficulties (80%), perceptual disturbances (75%), restlessness (76%), disorientation

(63%), anxiety (61%), paranoia (34%), hyper-excitability (27%), irritability (22%) and mental confusion (22%). The extent to which PCP posed serious problems at that time was indicated by the US Drug Abuse Warning Network (DAWN), a national reporting system for drug-related deaths and hospital emergencies. Data from the 662 participating emergency centres showed 111 events in October 1976 versus 54 events in October 1974; and reports of PCP-related deaths increased over roughly the same period from 17 in April 1976 to 30 in March 1977 (22). Undesirable psychological reactions were frequent. In a 1978 study at one urban psychiatric hospital, PCP was detected by blood analysis in 78.5% of 150 consecutive involuntary admissions (26).

Because PCP abuse occurred as a regional epidemic clear evidence of an association with formally diagnosable psychotic disorder emerged. In the mid- to late-1970's many case series reports of PCP-related psychotic disorder admitted to mental health services were published (e.g. 27-42), describing close temporal and regional associations between changes in illicit PCP production, levels of PCP abuse among young people, and changes in rates of emergency presentation of PCP-related psychotic disorder in this age group. Washington DC, a major centre for PCP production and abuse in the early 1970's, illustrates this point. The first hospital admissions for PCP psychosis occurred in late 1973. Thereafter, the admission rate increased rapidly to a peak in February 1974, when one-third of all first psychiatric admissions were diagnosed with PCP psychosis. In March 1974, police closure of a local illegal PCP laboratory resulted in a marked drop to no more than three new cases of PCP-related psychosis per month in April, May, and June 1974. A new epidemic of PCP psychosis occurred in 1975 and 1976. In early 1976 law enforcement agencies pronounced the Washington metropolitan area the PCP capital of the country, and increased raids on local illegal PCP laboratories. Thereafter a slow but steady decline in psychiatric admissions for PCP psychosis occurred (29).

Although a strong relationship between PCP abuse and psychotic disorder was evident, the face validity of PCP-induced psychosis as a model for schizophrenia also requires close phenomenological similarity between the two disorders. To make this comparison, three types of PCP-related conditions need to be distinguished: acute intoxication without

delirium (a 'bad trip'); acute intoxication with delirium; and the more persistent drug-induced psychotic disorder (38). Duration of acute PCP intoxication parallels the half-life of the drug. Symptom severity is dose-dependent. Acute intoxication without delirium lasts about 3-8 hours and presents with restlessness, agitation, hallucinations, delusions, nystagmus, hypertension, tachycardia, ataxia, slurred speech, and hyper-reflexia (38, 43, 44). PCP-induced delirium represents a more profound degree of toxicity, which can persist for a week. Dose-dependent clinical features include clouding of consciousness, disorientation, toxic psychosis, vomiting, hyper-salivation, spasticity, EEG slowing or seizures, and respiratory depression (33, 38, 43, 45, 46).

In addition to acute intoxication syndromes, PCP induces psychotic disorder that is very similar to schizophrenia or schizoaffective disorder in the absence of delirium (22, 27-29, 31, 32, 34, 36-38, 40, 41, 47-49). The duration of PCP-related psychosis bears no relationship to ingested dose or drug half-life. It characteristically shows sudden resolution within 2 to 4 weeks (29, 41), though on occasion persists for months. Patients with PCP-related psychosis could not be distinguished from schizophrenia patients on the basis of presenting symptoms (31, 33). All domains of schizophrenic symptomatology seemed to be represented. Prominent positive symptoms were reported: paranoia; and persecutory and grandiose delusions (31, 34, 36, 37, 39, 48, 50) often with bizarre Schneiderian qualities (33, 40, 51); and hallucinations in all modalities (31, 33-37, 39, 46, 48, 50). Formal thought disorder with loosening of associations, cognitive disorganization, perseveration or thought blocking occurred (27, 33, 34, 36-39, 50). Catatonic behaviour in a variety of forms was almost universally present with PCP-psychosis: inappropriate and unpredictable behaviour; excitement and violence; nudism; mannerisms and stereotypies; and catatonic posturing and mutism (13, 31, 33-41, 45, 46). Features resembling negative symptoms also occurred: blunted affect (46); apathy and emotional disengagement (38); social withdrawal and autistic behaviour (27, 31, 37); and amotivation (27, 31, 37, 38, 46).

Despite marked similarities between PCP psychosis and schizophrenia, cross-sectionally there were atypical features: a predominance of visual or haptic hallucinations over

auditory hallucinations; distortion of time appreciation and body image disturbance; and prominent somatosensory deficits, especially diminished proprioception and pain perception (19, 51, 52). As well, there were differences in psychiatric history with a relatively high proportion of patients not having a family history or personal history of schizophrenia, and an absence of previous psychiatric history or evidence of prodromal psychosocial deterioration (22, 28, 29, 38, 47, 49, 53). Although most cases of PCP-psychosis resolved within two weeks without sequelae (29), about 25% of patients went on to have a typical history of schizophrenia (37). This subgroup of patients took months rather than weeks to recover from the first PCP-related psychotic episode, tended to have a family history of schizophrenia, and a personal history of other psychiatric disorder (29, 31, 39).

A point of disagreement in the clinical literature concerns the effectiveness of dopamine D2 receptor (D2R) antagonist antipsychotics in the treatment of acute PCP psychosis. Some studies concluded benzodiazepines (13, 27, 33, 34, 45) were preferable to haloperidol or chlorpromazine in PCP intoxication whilst others favoured haloperidol (35, 42, 54, 55). Apart from one group (42, 55), most agreed that antipsychotic and sedatives may reduce agitation, however no pharmacological treatments appeared to shorten the course of the psychotic illness (13, 34). Luisada & Brown (37) noted that in the cases subsequently re-diagnosed with schizophrenia, acute response to antipsychotic drugs was faster and superior after re-diagnosis than during the first PCP-induced episode of psychosis. The equivocable response of PCP psychosis to D2R antagonists was the first clue that PCP psychosis may not be primarily linked to dopamine dysregulation.

Experimental studies using PCP in hospitalized patients with chronic schizophrenia supported the view that the psychotomimetic effect of PCP was directly related to mechanisms producing the symptoms of schizophrenia (56-58). Luby et al. (56) reported that immediately after IV PCP, patients showed an acute intensification of thought disorder and inappropriate affect: “it was as though … the acute phase of their illness had been reinstated”. Chronic patients frequently manifested symptom relapses persisting for more than a month after a single IV dose of PCP, indicating that PCP may act on a

fundamental disease process. That is, PCP exaggerated pre-existing, or precipitated an acute relapse of previously experienced, phenomenology rather than added qualitatively different psychotic symptoms. Response to PCP in patients was distinctly different to that with LSD or mescaline which produced a milder and brief change in the level of symptoms, mainly by adding qualitatively different symptoms such as kaleidoscopic visual hallucinations (49, 50, 56, 57). Providing the first suggestion that prefrontal mechanisms were directly related to PCP effects, Itil et al. (58) found that leucotomised patients with schizophrenia did not show as marked a response to PCP compared to un-leucotomised patients.

Experimental studies using PCP in human volunteers (HVs) also supported the view that PCP comprehensively induced symptoms resembling schizophrenia (52, 53, 56, 59, 60). Luby et al. (56) gave 9 HVs PCP in a subanaesthetic dose (0.1 mg/kg IV). All subjects experienced “body image changes” (impaired ability to distinguish between self and non-self stimuli, feelings of depersonalization, and a sense of unreality), “estrangement” (profound sense of aloneness or isolation, of being detached from the environment), and “disorganization of thought” (inability to maintain a set, frequent loss of goal ideas, impairment of abstract attitude, blocking, neologisms, word salad, and echolalia). Most subjects experienced negativism and hostility (child-like oppositional behaviour and catatonia-like reactions); and about one third showed repetitive motor behaviours (rhythmic body movements, including rocking, head-rolling, and grimacing). In another study of 12 HVs, PCP (0.075-0.1 mg/kg IV) induced positive symptoms (auditory hallucinations and thought disorder), negative symptoms (blunting, apathy and amotivation), catatonic features (psychomotor retardation, negativism and catatonic immobility), and cognitive deficits (associative learning and abstract reasoning deficits) (52). In contrast to LSD or mescaline, PCP in HVs induced perseveration and concreteness, and nystagmus: in common with LSD and mescaline, PCP induced body image disturbance, depersonalization, and disturbances in time appreciation (52). One study of seven HVs given 12 mg PCP by slow IV injection provided detailed descriptions of phenomenology (60). After a brief period of disorientation cleared, PCP caused marked cognitive deficits affecting “the function that combines, unifies, and integrates all

available information into a field which is meaningful" and preventing "goal-directed behaviour". Formal thought disorder (both loosening *and* concreteness) was apparent, including "catatonic-like perseveration". Sensory filtering deficits occurred so that the subject "was unable to focus actively on particular areas of his perceptual field [and] had become a victim of all inflowing stimuli but could not screen out the irrelevancies". Also, sensory distortions were experienced, like hearing your voice "seem to come from a distance – as if someone else were speaking" whilst intellectually knowing that it was yourself speaking. Feelings of passivity emerged so that "the subject saw his arms and legs move and yet did not have the feeling that he himself was making these movements". A profound sense of apathy and amotivation accompanied the PCP-induced psychotomimetic effects. Bakker and Amini (60) hypothesized that PCP produced a converse psychic state to that induced by LSD and psilocybin.

Moreover, early neurocognitive studies in HVs demonstrated PCP-induced deficits resembling those seen in schizophrenia. Rosenbaum et al. (53) compared three groups of HVs, 10 receiving PCP (0.1 mg/kg IV), 10 receiving LSD orally (1 ug/kg), and five receiving 500 mg amobarbital sodium IV (amphetamine 15 mg added to counter drowsiness associated with the barbiturate). Using a crude measure of attention, only PCP (i.e. not LSD or barbiturate) produced a deficit equivalent to that observed on the same test in patients with schizophrenia. On a motor learning task, the performance of only the PCP treated HVs dropped to the level of patients with schizophrenia. Cohen et al. (59) compared the effects of PCP, LSD and amobarbital sodium (amphetamine 15 mg added) in three groups of HVs. In a test of symbolic thinking (proverb interpretation), only PCP subjects (i.e. not LSD or barbiturate) showed deficits in symbolic thinking quantitatively equivalent to those seen in groups of patients with schizophrenia. Similar findings were made in relation to a test of sustained attention (serial sevens).

In summary, the psychotomimetic effects of PCP were first recognised as emergence phenomena when it was used as an anaesthetic. During a PCP abuse epidemic in the United States, it became evident that PCP induced formal psychotic disorder, even in individuals without evidence of predisposition to schizophrenia. The phenomenology of

the psychotomimetic effects of PCP were schizophrenia-like in range and quality, whether observed as anaesthetic emergence phenomena, presenting symptoms of PCP-induced psychotic disorder, or behavioural change induced by experimental use of PCP in patients with schizophrenia or HVs. Clinicians who observed PCP-induced symptoms recognised signs that Bleuler ('loosening' *plus* 'concreteness') and Kraepelin ('weakening…volition' *plus* 'loss of inner unity of the activities of intellect, emotion and volition') deemed primary to, and processes (e.g. sensorimotor gating, [61]) that psychologists considered characteristic of, schizophrenia. Because PCP was made illegal for use in human research in 1965, no studies measuring the effect of PCP on putative biomarkers of schizophrenia (e.g. prepulse inhibition [PPI], smooth pursuit eye movement [SPEM], P50 suppression or mismatch negativity [MMN]) or functional neuroimaging measures, were carried out in patients with schizophrenia or HVs. This type of human research had to await the introduction of ketamine, a safer and less potent psychotomimetic analogue of PCP.

Ketamine

Analogues of PCP were researched as alternative dissociative anaesthetic agents that might have fewer adverse reactions than PCP, the most important being ketamine [2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone]. Ketamine was first synthesised in 1961, first tested in human volunteers in 1964 (62), and first approved for general clinical use in 1970. It is used intravenously (analgesic dose, 1-2 mg/kg; anaesthetic dose, 5-10 mg/kg), intramuscularly (analgesic dose, 1.5-2mg/kg; anaesthetic dose, 4.0-6.0 mg/kg), and less frequently as an oral (100-300 mg/kg) anaesthetic (63, 64). Ketamine is highly lipid soluble and readily crosses the blood-brain barrier, inducing CNS effects within seconds of IV injection. The plasma half-life of ketamine has been reported to be 1-2 hours (65). When ketamine is used intravenously, duration of anaesthesia is dose-dependent and may be as brief as 30 minutes (66, 67) with complete recovery taking several hours. Because ketamine does not depress respiratory or cardiovascular systems, it was widely used as a field anaesthetic by the US army during the Vietnam War and continues to be marketed as a valuable anaesthetic for human procedures, especially in children, and in veterinarian practice.

While ketamine anaesthesia can produce emergence phenomena in up to 30% of anaesthetised adults, the symptoms are not as severe as those produced by PCP (49, 68). Emergence symptoms include alterations in mood state and body image, dissociative and out of body experiences, floating sensations, vivid dreams or illusions, 'weird trips', and occasionally delirium (64). Between 10-15% of post-operative patients show hallucinatory reactions (69, 70). Ketamine emergence phenomena are dose-dependent and age-related, with an incidence of less than 10% in patients less than 16 years old (64). Compared to standard anaesthesia (halothane/nitrous oxide), ketamine does not cause an excess of emergence reactions in children (71). In adults, pre-treatment with droperidol or haloperidol is inferior to benzodiazepines in preventing vivid emergence reactions and delirium following ketamine (reviewed in 64). In summary, when used as an anaesthetic ketamine induces emergent psychotomimetic effects qualitatively similar to PCP but quantitatively substantially less intense, in line with its more than 10-fold lower PCP-like activity (72) and about 30-fold lower NMDA receptor complex binding affinity (73, 74).

Despite warnings about its abuse potential (75), ketamine eventually appeared on the streets (known as 'Special K', 'Vitamin K' or 'K') in the early 1970's (25, 76) in the same way that PCP did in the 1960's. Ketamine use was popularised by publication accounts (77). In 1978 ketamine was authoritatively described as the "ultimate psychedelic" (78). Ketamine is typically inhaled or injected intramuscularly (79). Ketamine users try to achieve or 'fall into' a 'k-hole' of social detachment lasting up to an hour. This experience includes a distorted sense of space, so that a small room appears the size of a football field, and an indistinct awareness of time, so that a few minutes seems like an hour (80). Physical immobilization and disengagement from time and space is associated with psychedelic experiences such as spiritual journeys, interaction with famous or fictitious people, and hallucinatory visions. The k-hole ends abruptly though can quickly be re-entered with another injection of ketamine (79).

Unlike PCP, ketamine is difficult to manufacture and most recreational users acquire it through diversion of prescription product or theft from veterinary supplies (81). In the

1970's and 80's recreational use was restricted to a select group of the intelligentsia. Expanded use emerged in the context of the subcultural music phenomenon known as 'acid house music' and large scale parties called 'raves' (76, 82). Although there has been a growing number of reports of illicit use of ketamine in many countries (63), in comparison to other club drugs such as Ecstasy (MDMA), its use remains restricted to a small number of polysubstance abusers (81, 83). Currently, the lifetime prevalence of ketamine use is in the order of 0.7 – 2.6%, depending on the age and nationality of the study populations (83). Adverse events specifically related to illicit use of ketamine are difficult to ascertain because 80% of patients presenting to hospital emergency departments reporting ketamine use also report concurrent use of other drugs. Reasons for going to the emergency department include overdose (47%), unexpected reaction (28%), chronic effects (11%), or seeking detoxification (9%)(80).

Because there have been no regionally or temporally circumscribed epidemics of illicit ketamine use, it has been difficult to establish the psychiatric consequences of its abuse. The main evidence for a link between ketamine abuse and psychotic disorder is based on the occasional psychiatric case series report (e.g. 77, 84, 85); survey data of ketamine users who reported auditory hallucinations, paranoia, loose associations, and unusual thought content among the behavioural effects of ketamine (86); and psychometric data on small groups of ketamine users (87-90). Chronic ketamine abusers had higher scores on tests of delusional ideation and schizotypal symptomatology, which increased with acute dosing of ketamine (87-90), but also remained elevated at short-term follow-up (88, 89). The very limited literature on the neurocognitive effects of ketamine abuse suggests acute induction of impairments of working, episodic and semantic memory (89), and with chronic ketamine use, induction of chronic impairments in episodic memory (90). In summary, there is evidence of an association between ketamine abuse and increased proneness to quasi-psychotic symptoms and neurocognitive deficits, and psychotic disorder resembling schizophrenia, however the research supporting these associations is under-developed and does not define the strength of these associations.

In contrast to patient studies using PCP, experimental use of ketamine in hospitalised patients with chronic schizophrenia is considered ethically acceptable (91). This is partly based on experience using ketamine as an anaesthetic for surgery in patients with schizophrenia stabilised on antipsychotic medication, which was associated with only brief mild post-operative disturbance and not major psychotic relapse (92). Lahti et al. (93) gave subanaesthetic does of ketamine (0.1, 0.3 and 0.5 mg/kg IV) to 9 hospitalised patients with schizophrenia stabilised on haloperidol (0.3 mg/kg/day for at least 12 weeks). Six of the 9 patients were withdrawn from haloperidol for more than 4 weeks before being re-challenged with ketamine. In patients on haloperidol, ketamine induced 20 minutes post-injection about a 3-fold increase (dose-related) in BPRS psychosis scores, which returned to baseline within 90 minutes (though four out of the 9 patients reported delayed recurrence of psychotic symptoms for 24 hours after ketamine). In patients off haloperidol, ketamine induced dose-dependent increases in BPRS psychosis scores. Although ketamine-induced BPRS psychosis scores were slightly higher in patients off haloperidol compared with the same patients on haloperidol, it was clear that haloperidol provided little protection against the psychotomimetic effects of ketamine. Qualitatively there was remarkable similarity between the themes and content of psychotic symptoms induced by ketamine and symptoms associated with the patients' schizophrenic illness (93). In a replication study, Malhotra et al. (94) gave ketamine (0.77 mg/kg IV over one hour) to 13 hospitalised patients with schizophrenia and neuroleptic free for at least 2 weeks, and 16 HVs. In both unmedicated patients and HVs, ketamine produced significant increases in total BPRS scores, reflecting increased thought disorder and increased negative symptoms (withdrawal-retardation). Neurocognitive testing showed unmedicated patients and HVs both had significant ketamine-induced impairments in verbal recall and recognition memory, patients performing worse than HVs. When re-challenged with ketamine, patients subsequently stabilised on clozapine showed significantly blunted ketamine-induced increases in BPRS psychosis ratings (95). In another replication, Lahti et al. (96) gave ketamine (0.1, 0.3 and 0.5 mg/kg IV) to 17 hospitalised patients with schizophrenia stabilised on haloperidol (0.3 mg/kg/day for at least 12 weeks) and 18 HVs. Patients and HVs showed significant ketamine-induced increases on the three components of the BPRS psychosis score (thought disorder,

hallucinations, and delusions), and the BPRS withdrawal score, which reversed within 90 minutes post-injection. Approximately 70% of patients experienced ketamine-induced symptoms strikingly reminiscent of their usual psychotic symptoms during an illness exacerbation. In summary, unlike PCP the reaction to ketamine was mild and very brief in medicated patients, and more pronounced though still brief in unmedicated patients.

Experimental studies using ketamine in HVs have mainly focused on neurocognitive measurement. However, the recent challenge (97) to the view that ketamine is a psychotomimetic agent demands a brief review of the symptom-based literature. Ghoneim et al. (98) were the first to investigate the behavioural effects of subanaesthetic doses of ketamine in 34 HVs. Intramuscular ketamine (0.25 and 0.5 mg/kg) induced self-reported visual hallucinations (not auditory) in 75% of subjects at 0.25 mg/kg and 77% at 0.5 mg/kg. A minority of subjects also reported paranoid feelings of being manipulated or controlled during the experiment. In the second study, 18 HVs were given ketamine IV for 40 minutes (99). Ketamine 0.5 mg/kg (but not 0.1 mg/kg) induced significant increases in BPRS psychosis score 10 minutes from onset of the infusion until 15 minutes after the ketamine infusion was ceased. Ketamine significantly increased each of the four positive symptom sub-component scores (thought disorder, hallucinatory behaviour, suspiciousness, and unusual thought content or delusions). Hallucinatory behaviour was limited to illusionary experiences. Ketamine also induced significant increases in the BPRS hostility-suspiciousness factor score (hostility, suspiciousness, uncooperativeness, and grandiosity), and significant increases in BPRS negative symptoms. Comparable ketamine-induced symptoms to those noted in the two initial HVs studies have been observed in the many subsequent challenge studies (100-107). This comparability extended to the fine grained level of symptom structure, as was evident when the component structure of ketamine-induced conceptual disorganization in HVs was shown to closely overlap with the structure of formal thought disorder in patients with schizophrenia (101, 102). In summary, ketamine induces attenuated rather than frank hallucinations and delusions at the low doses typically used in experimental studies of HVs, and the impression that it is not psychotomimetic is inconsistent with the high rates

of emergence phenomena when used as an anaesthetic in adults and elicitation of frank psychotic symptoms when studied in patients with schizophrenia.

Experimental studies of the effects of ketamine in HVs confirm that ketamine-induced neurocognitive deficits show striking resemblance to those seen in schizophrenia (108, 109). In contrast to the crude assessments used in PCP studies, tests used in ketamine studies have good psychometric properties and can differentiate types of deficits (e.g., episodic versus working memory) and cognitive dysfunctions (e.g., encoding versus retrieval). Episodic memory (EM) refers to memory for events (sometimes called declarative or explicit memory). EM can be tested at the level of recall (generating a list of words or a story from memory) or recognition (deciding whether words have been previously presented). Deficits in recall may be caused by impaired encoding or retrieval of material; whilst deficits in recognition memory are caused by impaired encoding. EM deficits implicate medial temporal lobe structures, including the hippocampal formation. Prefrontal structures support higher order information processing such as: short-term online memory used to maintain and manipulate information (called working memory); executive functions (planning, decision making, and abstract reasoning); selective attention and vigilance; and verbal fluency. Psychomotor speed is particularly sensitive to prefrontal dysfunction. Inhibition is central to performing prefrontal-related tasks, which is subserved by intracortical circuits, and feedback loops with subcortical structures, especially the thalamus and basal ganglia (110-112).

Deficits in EM are consistently induced by ketamine in HVs (98, 99, 103, 107, 113-119), a result not seen with acute amphetamine challenge (104). A substantial literature indicates selective deficits at the level of encoding (recognition memory) rather than at the level of retrieval (99, 103, 107, 114, 119-122), a selective effect consistent with differential system dysfunction (123). Ketamine also induces deficits in working memory in HVs (100, 104, 107, 121, 124), with greater impact on manipulation compared with maintenance of information in working memory (108, 124), a distinction reviewed elsewhere (123). Deficits in working memory are not observed in acute amphetamine challenge (104). Ketamine induces deficits in other prefrontal functions including:

abstraction deficits in relation to proverb interpretation (115, 116); perseverative errors in sorting tasks (99, 115, 116); impaired response inhibition (119); and impaired vigilance (104, 116), the latter not seen with acute amphetamine challenge (104). Most studies show that ketamine induces deficits in selective attention (99, 103, 115, 125, 126), but not all (100, 107). Although only some studies report verbal fluency deficits (99, 100, 114, 116) and others do not (107, 115, 119, 127, 128), verbal fluency deficits are found in chronic ketamine recreational users (88, 89). Psychomotor speed is also slowed by ketamine (113, 121, 129). In summary, the pattern of neurocognitive deficits induced by ketamine resembles that seen in schizophrenia, and implicate dysfunction in the prefrontal cortex (130) and medial temporal lobe (131).

More proximal evidence that ketamine induces dysfunction in brain systems affected by schizophrenia has been provided by regional activation studies in HVs. Regional brain activation changes can be assessed using functional Magnetic Resonance Imaging (fMRI) to measure the Blood Oxygen Level Dependent (BOLD) effect, an index of regional cerebral blood flow (rCBF) change, and Positron Emission Tomography (PET) to measure changes in regional metabolic rate, either in terms of oxygen ([^{15}O]water) or glucose ([^{18}F]flurodeoxyglucose: FDG) uptake. As functional imaging studies of schizophrenia have more often than not found *reduced* activation prefrontally (e.g., 132, 133-135), especially in the cingulate cortex (e.g., 136, 137-140), and medial temporal lobe (e.g., 133, 135, 141), it was predicted that ketamine would induce *decreases* in regional brain activation in the same areas in HVs. However, contrary to hypothesis, acute ketamine dosing *increases* activation prefrontally (106, 142-147) including the cingulate cortex (106, 142, 147), and thalamus (106, 146-148). No studies reported changes in the hippocampus or medial temporal lobe. Two functional imaging studies of the effects of ketamine in patients with schizophrenia have been reported: one found ketamine-induced blood flow increases in frontal and cingulate regions (142); the other found ketamine-induced increases in rCBF in anterior cingulate and reduced rCBF in hippocampus (93).

Clinical biomarkers known to be abnormal in schizophrenia have also been assessed in experimental studies of ketamine in HVs. Contrary to expectation, deficits in prepulse inhibition (PPI) analogous to those seen in schizophrenia have not been observed in HVs administered ketamine (149, 150). Indeed, three independent studies showed PPI augmentation after ketamine administration to HVs (127, 151, 152). A single study of schizophrenia-like oculomotor abnormalities in HVs administered ketamine showed ketamine-induced smooth pursuit eye tracking deficits (114). Ketamine does not significantly reduce P50 suppression (149, 150). Deficits in MMN analogous to those observed in schizophrenia have been reported in HVs administered ketamine (153, 154).

To conclude, ketamine produces less potent PCP-like psychotomimetic effects commensurate with its more than 30-fold lower NMDA receptor complex binding activity (73, 74) compared with PCP. Qualitatively however, the two analogues induce equivalent psychotomimetic phenomena at the level of symptoms, neurocognition, and regional brain activation. It can be concluded therefore that ketamine challenge studies in HVs have face (and to a degree, construct) validity as preclinical models of PCP psychosis, and in turn as models of schizophrenia. Additional support for PCP-related models may be offered by comparing them with serotonergic models to examine evidence for discriminant validity. This will be sought by reviewing the psychotomimetic effects of the 5HT2A agonist, LSD, and the indirect serotonergic agonist, MDMA.

Lysergic acid diethylamide (LSD)

LSD (D-lysergic acid diethyamide) was originally synthesised in 1938 but its psychotomimetic effects were not discovered until 1943 when one of its co-discoverers experienced “fantastic visions of extraordinary vividness accompanied by a kaleidoscopic play of intense coloration” following inadvertent ingestion (155). LSD acts primarily as a functional agonist at the 5HT2A receptor (156). LSD quickly distributes to the brain and other body compartments, is metabolised in the liver and kidneys, and excreted in faeces. Effects of LSD are felt within an hour after ingestion and can last from 6 to 12 hours, although LSD cannot be detected in brain 20 minutes after ingestion. Oral psychotomimetic dosages are in the 25-150 μg range. Sensory perceptions are altered and

intensified so that colours appear brighter and sounds become magnified or perceived as patterns; there is a merging of senses (synesthesia) so that sounds become whirling patterns of vivid colour; perceptions of time and space are distorted, so that seconds may seems like an eternity, and objects become fluid and shifting. Depersonalisation; experience of feeling merged with another object or another person; hallucinations and visions; and religious revelations and spiritual insights, have been reported (157-159). That is, LSD intensifies emotional experience as much as perceptual experience (160). Physical effects are few and the lethal dose of LSD is so high that it has not been estimated. Psychological dependence is very uncommon (161). Physical dependence does not develop with LSD (162) however if used daily, tolerance to the psychotomimetic effects of LSD develops rapidly but disappears after a few days abstinence (157, 158). Legal production of LSD during the late 1940s and 1950s was directed towards research by the US Army (as a 'truth serum' or brain washing agent) and psychiatrists (as an adjunct to psychotherapy).

Around 1962 progressive restriction of legal use of LSD led to a dramatic increase in illegal production and illicit use throughout the US and internationally, promoted by the writings of a Harvard University instructor who became a media figure popularising LSD and the hippie movement with his catch phrase "Turn on, tune in and drop out" (155). The use of LSD peaked in the late 1960s and then steadily declined to a low but stable level in the 1970s. In the early to mid-1980s there appeared to be decreased interest in LSD, possibly due to reports of negative drug effects (163). Like ketamine, LSD re-emerged in the context of 'acid house' music and 'rave' parties (76, 82). In an European (164) and an Australian (165) study, prevalence of use was over 30% amongst youth attending rave or dance parties. Whilst the annual prevalence of illicit LSD use amongst high school students in the USA decreased from 1980 to 1990, in the mid-1990s prevalence again increased to almost 10% (163). However, probably due to efforts by law enforcement, use of LSD decreased to its lowest level in 2005 (163), paralleled by a significant decline in use among dance drug users, at least in the UK (166).

No epidemiological study has determined the relationship between LSD use and the incidence of psychotic disorder. Initially LSD was considered to have therapeutic value and reviews of its use with psychiatric supervision concluded that prolonged psychosis following LSD was rare (167-170). LSD therapy was initially applied to patients with an established history of schizophrenia with only a small risk of causing relapse (171, 172). However, following broader illicit use of LSD in the late 1960s a number of case series reports of psychosis in patients using LSD were published (reviewed by 173, 174, 175). Patients with psychotic disorder who had used LSD were said to present with phenomenologically similar symptoms and outcome to those with schizophrenia who did not take LSD (175-181). However, in contrast to patients with PCP-induced psychosis, most individuals presenting with psychosis in the setting of LSD abuse showed poor premorbid adjustment and/or prior psychiatric admissions (175-181) or family history of psychotic or other serious psychiatric illness (179, 182). Contemporary clinicians could not determine whether psychosis in the setting of LSD abuse was a separate diagnostic entity or simply represented a subgroup of patients with schizophrenia who used LSD. An important area of agreement in the clinical literature was the view that the symptoms of acute LSD intoxication were phenomenologically different to the symptoms of schizophrenia (183-186). LSD-induced perceptual disorders are visual rather than auditory; the visual distortions are not frank hallucinations but have the character of illusions; delusional ideation is not stable and usually insight is retained; negative symptoms are at most mild; and, LSD-induced phenomenology is often distinguishable by patients with schizophrenia from their primary symptoms (183-186). In marked contrast to both schizophrenia and PCP psychosis, the hallucinogenic effects of acute LSD intoxication subside rapidly with benzodiazepines (44) unless delirium is evident. Other dissimilarities with schizophrenia were reported in LSD-related (N,N-dimethyltryptamine [DMT] or psilocybin) challenge studies in HVs measuring PPI (151, 187, 188) or MMN (189, 190) which did not find deficits, although deficits in attention (126) and P50 suppression (187) with DMT were reported.

In conclusion, although LSD has obvious hallucinogenic effects, it is debatable whether it should be considered psychotogenic. Indeed, support for the existence of psychotic

disorder specifically induced by LSD as a diagnostic entity is inconclusive. Despite periods of relatively high and low rates of use of LSD in communities, no formal or informal epidemiological data have linked fluctuations in community use to variations in the incidence of psychotic disorder. In fact, only a total of 75 individual case reports of putative LSD-psychosis were found in a recent world-wide review (175). The occurrence of psychosis in the setting of LSD abuse appears to be more related to individual vulnerabilities than specific drug actions. This does not mean that adverse events with LSD do not occur (174). Acute LSD intoxication is associated with panic attacks and harm from misadventure, and a long-term consequence, Hallucinogen Persisting Perception Disorder (HPPD) or 'flashbacks', has diagnostic validity (191). Nonetheless, models based on LSD-related drugs are not irrelevant to the study of schizophrenia, especially to investigate disturbances in serotonergic regulation (192, 193), because of the 5HT2A receptor antagonist actions of atypical antipsychotics (186, 194, 195), and the potential relevance of interactions between glutamatergic and serotonergic systems in the pathogenesis of schizophrenia (126, 156, 196-199). An example of this type of interaction is the recent discovery that functional complexes form between 5HT2A receptors and group II metabotropic glutamate receptors (mGluR2) in brain cortex, complexes which are targeted by LSD (200). For the purposes of this review however at this stage we conclude our formal consideration of LSD-induced psychotomimetic effects as a model of schizophrenia.

Ecstasy

MDMA (3,4-methylenedioxy-methamphetamine) is a ring-substituted amphetamine derivative. It was patented in 1914 but never made commercially available. MDMA was classified a restricted drug in the United Kingdom in 1977 and in the United States in 1985. MDMA is almost always consumed orally, the psychoactive dose being about 100 mg. The primary effect of MDMA is to produce a positive mood state with feelings of euphoria, intimacy and closeness to other people, an effect that distinguishes it from amphetamine or hallucinogens (201). MDMA also has stimulant effects as well as mild psychedelic effects on insight and perceptual and sensual enhancement. The peak psychoactive effects last on average 4-6 hours, though the half-life of MDMA is

approximately 9 hours in humans (202). Tolerance to the psychoactive effects develops rapidly (203). No physical withdrawal syndrome has been described (204), but psychological dependence is common (161, 205, 206). Illicit Ecstasy tablets often contain compounds related to MDMA, such as MDE (3,4-methylenedioxy-methamphetamine). The generic term 'Ecstasy' is now preferred because it may refer to MDMA, analogues of MDMA, or a combination of these (207). Ecstasy use by young people has worldwide popularity (208, 209). In the United Kingdom during the mid-1980s the drug of choice for people attending raves was Ecstasy and the popularity of this youth culture resulted in an explosion in recreational use. Among US college students there was a steady increase in Ecstasy use from 2.0% in 1991 to 13.1% in 2000 (210). Similarly, in the Australian general population there is a steady increase in the proportion of people who have ever tried Ecstasy from 4.8% in 1998, 6.1% in 2001, to 7.5% in 2004 (211, 212). Amongst dance or rave party attendees, the use of Ecstasy is far more common (up to 80% prevalence) than the use of ketamine and PCP (83, 164, 165); however, polysubstance abuse (especially methamphetamine, cannabis and hallucinogens) among Ecstasy users is the norm (80, 213-215).

Public alarm concerning the dangers of Ecstasy use initially arose from reports of sudden death in young healthy users, especially when ingestion occurred at dance parties which were typically hot, crowded venues with loud repetitive music and light shows (216, 217). Cause of death was either cardiac arrhythmia or malignant hyperthermia, and usually related to polysubstance ingestion (218). However, a direct link between the fatalities and Ecstasy use is supported by a strong correlation between rates of Ecstasy use and rates of fatalities (219). Milder effects of intoxication include nausea, loss of appetite, tachycardia, hypertension, jaw tension, bruxism and sweating (215). Chronic adverse events associated with Ecstasy use include extensive polydrug use, high rates of intravenous drug use, and financial, relationship and occupational problems (214).

Of particular concern is evidence of associations between Ecstasy use and neurocognitive deficits. These associations remain controversial. Although there are several cross-sectional studies showing cognitive impairment in Ecstasy users (reviewed in 220), there

is evidence that these impairments may be due to polysubstance abuse rather than Ecstasy use itself (221, 222). Although the evidence from longitudinal studies for an association between chronic Ecstasy use and long-term neurocognitive impairment is fairly consistent (223), this association also remains controversial. In a major review, Morgan (220) concluded that in many longitudinal studies the evidence for an association between selective memory impairments and chronic heavy recreational use of Ecstasy may be confounded by polysubstance abuse. There are studies showing a correlation between the total dose of MDMA exposure and memory performance (224-226), but again this association is open to confounding by polysubstance abuse. Moreover, a consistent profile of neurocognitive deficits in Ecstasy users is not evident, some reporting mainly prefrontal deficits (e.g. 227), others observing mainly hippocampal-related memory deficits (228), whilst others find both (226). In summary, researchers hold polarised views on the harm of Ecstasy use seemingly reflecting divided public opinion, with some concluding evidence of harm is definitive (229, 230) whilst others are equally certain that evidence of harm is inconclusive or absent (208).

Although there are many studies reporting an association between Ecstasy use and mental disorder (especially depression and anxiety), it is impossible to determine in cross-sectional studies whether this relationship is due to Ecstasy, associated polysubstance abuse (208), and whether it pre- or post-dates Ecstasy use. In prospective (231) or retrospective (232) comparisons of the age-of-onset of mental disorder and age-of-onset of Ecstasy use, psychiatric disorder appeared to precede Ecstasy consumption. A meta-analysis showed that the strength of the association between Ecstasy use and depressive symptomatology was weak and unlikely to be clinically relevant (233).

Psychotic disorder as an adverse reaction to Ecstasy use appears to be rare and idiosyncratic, mainly determined by user-related variables (familial predisposition; previous psychotic episodes; very high dose exposure; and polysubstance abuse) rather than be drug-related. Soar et al. (234) reviewed published psychiatric case studies from the previous 10 years involving MDMA. Of the 38 cases, 22 had a psychotic disorder or symptoms. Two of this subgroup had a family history of psychosis, an observed rate that

is precisely comparable to the expected rate with schizophrenia itself. As well, in the psychotic patients confounding arose from greater Ecstasy use being associated with heavier polysubstance use. In an Italian series (235) of 32 cases of psychotic disorder in Ecstasy users (patients with self-reported polysubstance abuse excluded), symptomatology was not phenomenologically distinctive, and many cases had a family history of psychiatric disorder or past personal history of non-psychotic psychiatric disorder, making it impossible to determine whether Ecstasy was the primary cause of psychosis or not. In a community sample, the occurrence of schizophrenia was not related to heavy Ecstasy exposure (232). There is only a single case report in which experimental MDMA intoxication produced an acute toxic hallucinosis lasting 2.5 hours (236), emphasising the rarity and idiosyncratic nature of this adverse event. The lack of evidence of an association between psychotic disorder and Ecstasy use described above has not prevented opinion being published that Ecstasy "has a special risk for persistent organic psychoses" (229). Clinical biomarker studies have not supported MDMA challenge as a model of schizophrenia. Unexpected increases (i.e., not deficits) in PPI have been observed after administration of MDMA in HVs (237, 238) and in chronic ecstasy abusers (239). Therefore, for the purposes of this review at this stage we conclude our formal consideration of MDMA-induced psychotomimetic effects as a model of schizophrenia.

Animal studies

This Section reviews animal models induced by PCP and analogues to further assess the construct and predictive validity of the PCP model of schizophrenia. We examine how closely these animal models replicate pathophysiological and theoretical processes hypothesised to underlie schizophrenia. Evidence of predictive validity is presented by comparing the potency of novel compounds in reversing PCP-related psychotomimetic effects in the model with their antipsychotic effect in patients with schizophrenia. First, principles and constraints concerning disease modelling in animals are noted, and illustrated by considering the amphetamine-induced model of psychosis.

Animal modelling: Principles and constraints

Attempts at modelling psychiatric diseases in their entirety is futile because rodents have much simpler brain structure than humans, making it impossible for rodents to display the same kinds of complex symptoms as humans: it is unrealistic to expect homology on *all* aspects of a disorder across two species (1, 240). A more feasible approach is to model specific signs or symptoms of the disease, or neurobiological correlates, for which there are relatively equivalent behaviours or measures in both humans and rodents. This approach is illustrated by the dominant animal model for schizophrenia, amphetamine-induced hyperlocomotion in rodents, a model that currently serves as the 'gold standard' in evaluating other models, especially the PCP model.

Amphetamine-induced hyperlocomotion in animals has face validity because the stereotypic hyperactivation of the model bears 'symptom similarity' to the agitation seen in patients with acute schizophrenia, and in turn, because amphetamine abuse is associated with psychotic disorder resembling schizophrenia in humans (241). The model also has high predictive validity because currently available antipsychotic drugs attenuate amphetamine-induced hyperlocomotion in rodents. The limitation of using hyperlocomotion as the measure of the model is that this behaviour is also reversed by compounds that have no antipsychotic effect clinically, and the compound with superior antipsychotic effect, clozapine, is no more effective in reversing hyperlocomotion than the conventional D2R antagonist, haloperidol (242). The dangers of basing animal models on symptom similarity using analogous behavioural measurement have been long recognised (243). A limitation with using a model that has high predictive validity for a single class of drugs is 'pharmacological isomorphism', the utility of the model being limited to identifying only one class of ('me-too') drugs and not supporting the discovery of drugs of a distinctly new class (9). The construct validity of amphetamine-induced animal models of schizophrenia has been augmented by measurement of disease markers, such as deficits in PPI. PPI is an example of reliable measurement of an indicator of human disease (also putatively indexing a theoretical process, 'sensorimotor gating', (61)) that has an equivalent measureable behaviour in the animal model ('homologous'

measurement, 243). However, the disease non-specificity of PPI and hyperlocomotion constrains their utility in animal studies of the pathophysiology of schizophrenia.

This constraint has been addressed in amphetamine-induced animal models by measuring brain system/neuronal dysfunctions, in addition to assessing behavioural change. A step in this direction was based on findings in rodents and primates that induction of hyperlocomotion by dopamine agonists (e.g. amphetamine) is related to increased subcortical dopamine release in ventral striatum (244-249). Notably, these preclinical findings informed research that produced the first direct evidence in living patients of significant dysregulation of subcortical dopamine neurotransmission in schizophrenia using an *in vivo* receptor binding method (250), a consistently confirmed finding (reviewed in 251). Patients show amphetamine-induced sensitivity to presynaptic dopamine release resulting from inhibition of the dopamine transport (DAT) and the vesicular monoamine transporter (VMAT). Increases in positive (but not negative) symptoms in patients following amphetamine challenge were found to correlate with *in vivo* dopamine release (252). That is, a neurobiological correlate of the animal model correctly predicted the nature of the dopaminergic dysregulation later found in patients with schizophrenia.

Recent research on amphetamine-induced animal models has revealed abnormalities at the neuronal level in prefrontal cortex (253). Homayoun and Moghaddam (253) investigated PFC neuronal activation in rats after amphetamine sensitisation (five days repeated daily dosing). Emphasising the importance of specifying pharmacological models in terms of exposure to single (acute) or repeated (subchronic or chronic) dosing, this group reported that the electrophysiological responses of PFC neurons begin to change after a few doses of amphetamine. Repeated amphetamine exposure had opposite effects in two regions of prefrontal cortex – a progressive hyperactivation of orbitofrontal cortex and hypoactivation of medial prefrontal cortex. These alterations were present irrespective of whether the rats were behaving spontaneously or performing an operant responding task, indicating they were not secondary to hyperlocomotion. The pattern of prefrontal findings is homologous to prefrontal findings reported in human *in vivo*

neuroimaging studies of schizophrenia (hypoactivation of dorsolateral PFC, 254) and substance addiction (hyperactivation of orbitofrontal cortex, 255), another example of the animal model informing human disease research. As only subchronic or chronic amphetamine dosing (256-261), and not single dosing, induces psychosis in healthy or substance-abusing volunteers, prefrontal neuronal dysfunction demonstrated in the repeat-dosing amphetamine model (253) may be of pathophysiological importance to schizophrenia, providing a marker for identifying novel and more specific pharmacotherapies, as well as sign-posting future research into prefrontal neuronal dysfunction in patients with schizophrenia. Linking the repeat-dosing amphetamine model back to the PCP model of schizophrenia are studies showing that psychostimulant sensitisation (both behavioural and neurochemical) is mediated by NMDA and non-NMDA glutamate-dependent processes secondary to increased stimulant-induced dopamine release (262-264).

In summary, lessons from the extensive characterisation of the amphetamine-induced model of schizophrenia are relevant to evaluating other animal models. For example PCP-related models are also sensitive to dosing schedule, with chronic (repeated daily) dosing inducing hypoactivation (265), not hyperactivation as seen in acute (single) dosing models. An issue of utmost importance is characterising an animal model at the neuronal and brain tissue level (8, 266). This level of information is the basis of a model's capacity to generate predictions about human pathophysiology and likely clinical effectiveness of novel pharmacotherapies (4, 7, 266, 267). These issues are as relevant to the burgeoning literature on genetically modified models (1, 2, 4), as they are to the evaluation of PCP-related animal models, the subject to which we now proceed.

Animal models and controversy about the pharmacology of PCP and its analogues

Animal studies use a range of PCP analogues, all of which are considered to have their primary pharmacological action at a binding site located within the ion channel formed by the NMDA glutamatergic receptor (called 'the PCP binding site'). PCP inhibits NMDA receptor-mediated neurotransmitter release and therefore functions as an NMDA

receptor antagonist. As PCP binds to a site of the NMDA receptor complex that is distinct from the recognition site for the neurotransmitter glutamate, its inhibitory effects are non-competitive in that they cannot be overcome by increased neurotransmitter concentrations. PCP analogues, ketamine and MK-801 (dizocilpine), also have high affinity for the PCP binding site and are NMDA antagonists. Compared to PCP, ketamine has lower affinity and MK-801 higher affinity for the PCP binding site. Although PCP and ketamine interacts with catecholamine re-uptake transporters at anaesthetic doses, psychotomimetic effects occur at lower serum levels where these agents have appreciable affinity only at the NMDA receptor complex (72).

A leading research group has argued that the psychotomimetic effects of PCP and ketamine are primarily mediated by direct actions on dopaminergic transmission (268-273). They propose that all psychotomimetic drugs exert this effect via D2R-related action (274). This group presented *in vitro* experimental evidence that PCP and ketamine are potent ligands at striatal D2R in the high-affinity state (269, 272, 273). No other group has replicated these findings, which have been contradicted (275) or refuted either in a functional assay (276) or other experiments (277, 278). Another source of evidence that is in complete disagreement with the hypothesis that the psychotomimetic effects of PCP analogues are directly caused by an amphetamine-like striatal dopaminergic dysregulation, are the negative results reported in the substantial *in vivo* ligand binding imaging literature (reviewed in 279). In contrast to PCP and ketamine, MK-801 is highly selective for the PCP site even at very high concentrations, yet it has strong psychotomimetic effects (72) as does the highly selective competitive NMDA antagonist, CGS 19755 (Selfotel, 280). Moreover, drug discrimination studies, in which animals are trained to recognise drugs with a common pharmacological effect, demonstrate that MK-801 and ketamine have PCP–like effects directly proportional to their binding affinity potency at the PCP site and these effects are not related to the differential affinity of these drugs for catecholamine transporters, which are only evident at anaesthetic doses (reviewed in 72). It can therefore be confidently concluded that the primary pharmacological action responsible for the psychotomimetic effects of PCP and analogues is non-competitive antagonism of the NMDA receptor complex, and any

disturbance of dopaminergic systems is secondary to and downstream from, glutamatergic antagonism.

Changes in behaviour and clinical biomarkers in PCP-related models

As discussed above, amphetamine-induced hyperlocomotion in animal models represents analogous measurement of the psychotomimetic effects of amphetamine seen in humans. It is assumed that hyperlocomotion in animal models of psychosis is analogous to the positive symptoms of schizophrenia, an assumption supported by antipsychotic-induced attenuation of hyperlocomotion in animal models, and positive symptoms in patients. However, analogous measurement in models may have no relationship to disease pathophysiology (9). PCP (e.g., 281, 282-286), ketamine (e.g., 287), and MK-801 (e.g., 266, 288) also induce hyperlocomotion in animals, illustrating that two different pharmacological models show the same analogous behaviour. However if a characteristic sign of the human disease, such as a distinctive catatonia-like stereotopy, selective impairment in working memory, or a specific deficit in sensorimotor gating, is assessed across species using homologous measurement, it is more likely that aspects of construct validity will be measured. PCP induces characteristic stereotypic head movements in humans (see above), which are replicated in animal models treated with PCP (e.g., 281, 286), ketamine (e.g., 287, 289) or MK-801 (e.g., 266). That is, hyperlocomotion is common to both PCP and amphetamine models, whereas only PCP and analogues induce head movements that are identical to PCP-induced stereotopies in humans and similar to catatonia-like motor changes in schizophrenia. Additional face validity for PCP-induced animal models for schizophrenia relates to measurement of PCP-induced ‘negative’ symptoms. In contrast to acute amphetamine-induced models that do not show homologous behaviour to negative symptoms (282, 284, 288), animal models induced by PCP (282-285, 290) and MK-801 (288) show deficits in social interaction, considered to be homologous to negative symptoms.

Neurocognitive testing of PCP-related animal models also supports the face (and to a degree, construct) validity of these models, demonstrating homologous deficits to those seen in PCP psychosis and schizophrenia. In particular, behavioural assessment of

animals treated with PCP (281, 291-294) or MK-801 (266, 295, 296) reveal deficits on prefrontal-related tests, such as spatial working memory tasks (266, 281, 291, 293, 294, 296) and executive function tasks, the latter eliciting perserverative responding and difficulties in set shifting (292, 295). Moreover, measures of clinical biomarkers in animal models induced by PCP (297-299), ketamine (300, 301) and MK-801 (297, 298) have demonstrated deficits in PPI homologous to those found in schizophrenia. Whereas pre-treatment of rats with haloperidol attenuates PPI deficits induced by dopamine agonists (302, 303), haloperidol has no significant effect on the ability of PCP (299), ketamine (300), or MK-801 (299) to disrupt PPI. Taken together, these findings indicate that PPI deficits associated with the amphetamine-induced model are mediated by subcortical D2R, and PPI deficits associated with PCP-related models are not, a form of discriminant validity.

Increased regional brain activation in acute PCP-related animal models

Face (and to a degree, construct) validity of PCP-related animal models would be supported if homologous patterns of brain activation were seen across animal models, PCP-induced psychosis, and schizophrenia. Homology of activation change could be expected in terms of both regional distribution, and whether it is under- or over-activated. Animal models induced by MK-801 (304) or ketamine (304-306) show altered 2DG activation in: frontal regions, especially medial prefrontal and retrosplenial (cingulate) cortex; medial temporal regions, especially the hippocampal formation; anterior ventral thalamic nucleus; and subcortical limbic centres. Areas of altered BOLD contrast in ketamine-induced animal models included frontal regions and the hippocampal formation (307, 308). Against prediction, regional activation indexed by either BOLD contrast or 2DG autoradiography is *increased* in animal models induced by MK-801 and ketamine in acute (single) doses (304-308). In summary, distribution of hyperactivation in PCP-related animal models shows regional homology with activation abnormalities reported in studies of patients with schizophrenia, implicating four specific brain regions, namely: prefrontal cortex (309-312), hippocampal formation (313, 314), subcortical limbic nuclei (315, 316), and thalamic nuclei (137, 139, 317).

Paradoxical *hyperactivation* seen in PCP-related animal models, compared to the *hypoactivation* usually reported in studies of patients, is of special interest. Possible causes of animal model-human disease discrepancies include mismatch in a number of areas 1) use of acute pharmacological challenges to model chronic brain disease 2) use of neurochemical challenges to model neurodevelopmental disorder 3) modelling a different stage of the human disease in an animal, compared to the disease stage in which human findings were made (e.g. early-stage model versus late-stage disease) and 4) modelling different phases of the disease (e.g. acute relapse versus inter-episode residua). Two lines of evidence suggest that the direction-of-activation discrepancy may be due to administration of an acute (single) dose of PCP or analogue to model chronic disease findings. First, PET studies in humans show that a single dose of ketamine induced *increased* brain activation (146, 147), whilst PET studies of subjects who chronically abused PCP showed *reduced* brain activation (318, 319). Second, *reduced* prefrontal and thalamic reticulate nucleus activation was found using 2DG in a repeat-dosing animal model (320). Although these findings suggest that there is not a real discrepancy between the clinical and preclinical models, the intriguing question remains as to why NMDA antagonists should induce brain hyperactivation.

Increased prefrontal glutamate in PCP-related animal models

Using microdialysis in rats, Moghaddam and Adams (281, 321) showed that PCP induces presynaptic release of glutamate and dopamine, both showing increased extracellular levels in prefrontal cortex and nucleus accumbens. In this landmark study (see commentary in 321) a single dose of PCP (5 mg/kg IP) elicited marked motor activity, stereotopy with head rolling, and spatial working memory impairments. By manipulating the level of extracellular glutamate (whilst not altering dopamine levels) with a mGluR agonist (see next Section), these authors demonstrated that psychotomimetic behaviour of the model (hyperlocomotion and stereotopy) were related to glutamate levels, not dopamine levels. Increased prefrontal/hippocampal/subcortical glutamate efflux is a consistent effect replicated with a range of NMDA antagonists, including ketamine (322), PCP (323), and a competitive antagonist (324). Taken together, the work of Moghaddam

and colleagues has characterised a key element of the neuronal dysfunction underlying psychotomimetic behaviour in this animal model – increased levels of extracellular glutamate and dopamine. But is glutamate efflux related to prefrontal hyperactivation at the neuronal level?

Increased prefrontal neuronal firing in PCP-related animal models

Another cornerstone in our understanding of the cellular mechanism of the PCP-induced animal model concerns the firing rate of prefrontal neurons. Jackson et al. (266) administered single systemic doses of MK-801 (0.01, 0.05, 0.1 and 0.3 mg/kg) to rats. At the two highest doses of MK-801 sustained and substantial increases in prefrontal neuron firing occurred, firing rates highly correlated with stereotopy counts. MK-801 also induced spatial working memory deficits. These important *in vivo* findings, demonstrating that MK-801-induced increases in firing rate in prefrontal neurons are directly related to behavioural measures of the animal model, have been replicated (325-327). Two other studies from the Fukushima Medical University, one of which represented the first demonstration of the effect of PCP on prefrontal neuron firing rate (328), add important detail to the description of the PCP-induced cellular dysfunction. Suzuki et al. (328) found a differential effect on prefrontal neuronal firing between systemic and locally (prefrontally) administered PCP, indicating that afferents (presumably non-NMDA glutamate) from other brain regions partly drive the prefrontal neuronal firing. This hypothesis was supported by a subsequent study showing that PCP applied locally to the ventral hippocampus led to increased prefrontal neuronal firing (329), apparently mediated by AMPA/kainate glutamate receptors (330). The thalamocortical circuit may also be a major driver of pathological prefrontal activation and increased cortical glutamate release. MK-801 injections into the anterior nucleus of the thalamus induced cortical degeneration in a pattern indistinguishable from systemic administration, while injection directly into cortical regions did not lead to degenerative change (112). As glutamatergic systems are the major energy users in the brain, and pyramidal cells are the major excitatory cell type, it is likely that PCP-induced regional hyperactivation indexed by BOLD or 2DG uptake is related to increases in pyramidal cell firing. The question as to how NMDA antagonism induces increased extracellular

glutamate and dopamine, and increased prefrontal neuronal firing, remains to be considered.

GABAergic interneuron deficits in PCP-related animal models

A long held assumption about the PCP model of psychosis is that deficits in GABAergic interneuron transmission, presumed to be related to PCP-induced dysfunction of the NMDA receptor complex on GABAergic neurons, results in disinhibition of pyramidal cells (3, 109, 112, 156, 331-338). There is now a wealth of evidence to support this assumption. Parvalbumin (PV) is a calcium binding protein located within a subpopulation of GABAergic interneurons. PV interneurons receive the largest glutamatergic input among all GABA-releasing neurons in cortex (339) and are highly sensitive to NMDA antagonists (340), a property related to the role played by NMDA receptors in control of basal synaptic activation of these interneurons (341). In an acute PCP dosing rat study, expression of PV was decreased in the reticular nucleus of the thalamus and substantia nigra pars reticulate (342). In repeat-dosing rat models, the density or number of hippocampal GABAergic interneurons expressing PV was decreased with PCP (296, 343) and with ketamine (344). In a repeat-dosing PCP monkey model, the density of prefrontal PV containing axo-axonic structures was decreased (345). Also, ketamine induced dose-dependent decreases in PV and GAD67 immuno-reactivity in cultured PV interneurons specifically (346, 347). Because PV interneurons are involved in the generation of gamma oscillations responsible for temporal encoding and storage or recall of information required for working memory (348), alterations in gamma frequencies have been used to index functional deficits in GABAergic interneurons induced by ketamine (349). Juvenile rats given MK-801 for 14 days that showed increased firing of pyramidal cells and deficits in spatial memory pre-mortem, also showed decreased numbers of PV interneurons postmortem (296). A recent study provided the first direct evidence of an inverse relationship between MK-801-induced increases in prefrontal pyramidal cell firing rate and decreases in activity of GABAergic interneurons (326). This important study (326) demonstrated that NMDA receptors preferentially drive the activity of cortical inhibitory interneurons, and that NMDA

receptor antagonism causes cortical excitation by disinhibition of prefrontal pyramidal neurons.

The significance of the cellular dysfunctions affecting GABAergic interneurons in PCP-related animal models pertains to reports of homologous changes in prefrontal PV interneurons in postmortem studies of schizophrenia (309-312, 350). Moreover, disturbances in the gamma frequency band of scalp-recorded EEG, considered to reflect gamma oscillations arising from PV interneuron cortical synchronisation, are evident in schizophrenia and correlated with prefrontal-related cognitive deficits in patients (351-354). That is, the PCP model of schizophrenia offers sufficient construct validity at the level of cellular dysfunction to inform hypotheses about the pathophysiology of schizophrenia that can be tested in the model. An example of such a hypothesis concerns the possibility that reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activation may be involved in the loss of PV expression in prefrontal cortex in schizophrenia (346). This hypothesis arose directly from a study of the animal model, and awaits investigation in studies of the human disease itself.

Secondary monoaminergic system disturbances in PCP-related animal models

Another component of the cellular dysfunction related to the PCP model concerns secondary effects of NMDA antagonism on catecholaminergic and serotonergic pathways. As noted above, there is little evidence of direct action on these neurotransmitter systems. However, there is a wealth of evidence that glutamatergic systems closely interact with dopaminergic (293, 294, 336, 355) and serotonergic (156, 196, 197, 199, 356) pathways. In a series of ground-breaking studies Jentsch and colleagues showed that acute PCP dosing induces marked increases in prefrontal dopamine turnover (355), whilst daily chronic (14 days) dosing causes significantly reduced prefrontal dopamine utilisation (293) that persists up to four weeks after ceasing PCP administration (294). This laboratory showed that chronic PCP-induced decreased dopamine utilisation was associated with deficits in spatial learning memory in rats (293), and with deficits in perseverative learning in monkeys (294). These findings illustrate the

importance of specifying acute or chronic exposure to PCP and analogues in describing the animal model (265). Glutamatergic-serotonergic system interactions are also of relevance, increased prefrontal glutamate efflux being induced by 5HT2A receptor activation presynaptically (126, 194, 357, 358) and the psychotomimetic effects of LSD being reversed by mGluR2 agonist reduction of glutamate efflux (200).

In summary, the PCP model of schizophrenia is now supported by an extensive literature describing model-induced animal behaviour and neurocognitive deficits, regional brain activation patterns, and a comprehensive range of cellular dysfunctions. Advanced *in vitro* and *in vivo* assays applied to this animal model permit a high level of homologous measurement. Novel hypotheses about pathogenesis and pathophysiology have been generated based on the model, which now go well beyond generalisations about hypoglutamatergic function in schizophrenia (359-363). Ultimately however, the most important form of validity is whether the model can predict antipsychotic efficacy in the development of new medications for schizophrenia.

Drug development using PCP-related animal models

Animal models with predictive validity, coupled with knowledge of drug action, are powerful combinations in the study of schizophrenia and drug development (338). For the purposes of this Section, mainly drugs that have been tested in patients to determine efficacy will be reviewed. Predictive validity will be assessed on the basis of whether PCP-related models can differentiate between clozapine and other available antipsychotics; and whether the model is predictive of novel treatments that are not based on D2R antagonism.

There are now several studies that demonstrate differential response to clozapine compared to other antipsychotic agents using the PCP animal model. To illustrate, in an acute ketamine-induced model, clozapine completely blocked all ketamine-induced regional brain activation (indexed by 2DG uptake), an effect not seen with haloperidol (305); and in a PCP repeat–dosing model, clozapine but not haloperidol reversed PCP-induced prelimbic reductions in PV staining (320). The reader is reminded that

amphetamine-induced models did not behaviourally differentiate the effect of clozapine and haloperidol (242). Of greater importance however, is the predictive validity of the model in relation to novel drug development, drugs that are not simply variations of those based on D2R antagonism.

The first indication that the PCP-induced model might have predictive validity for agents with novel modes of action concerns the anticonvulsant, lamotrigine. Lamotrigine inhibits glutamate release via blockade of sodium channels. When tested in a ketamine-induced mouse model, lamotrigine reversed ketamine-induced PPI deficits, an effect it did not have on amphetamine-induced PPI deficits (301). Moreover, lamotrigine reduced ketamine-induced perceptual abnormalities in HVs (364). Although lamotrigine is not effective as monotherapy in patients with schizophrenia, when used in treatment-resistant patients to augment D2R antagonist antipsychotics (365-367), lamotrigine does have modest beneficial effects that are evident to a greater extend when used in conjunction with clozapine (368-370). Carbamazapine, which does not appreciably reduce glutamate release despite its similar action to lamotrigine in blocking sodium channels (371), is ineffective as an augmenting agent in treatment-resistant schizophrenia (372).

Of greater interest is the predictive validity of the PCP animal model in relation to new drugs that act directly on glutamate. Preliminary evidence that NMDA receptor complex modulators might be efficacious in schizophrenia came from studies demonstrating small beneficial effects of augmenting antipsychotic treatment with glycine or serine (reviewed in 360). Based on the PCP model, researchers have now identified and tested a range of new and promising compounds. Amongst these is sarcosine, a glycine transporter 1 (Glyt-1) inhibitor, which increases glycine at the NMDA receptor complex, thereby facilitating NMDA transmission. Preclinical testing on PCP-induced models showed reversal of PCP effects (373), not as apparent in the amphetamine-induced model. Subsequent clinical testing revealed that sarcosine was ineffective as monotherapy (374), but that it shows a significant beneficial effect when used as an augmenting agent with conventional antipsychotic treatment (375). Sarcosine did not offer additional benefit as an adjunct treatment with clozapine (376), suggesting that clozapine may have direct

action at Glyt-1. Another example of drug development based on the PCP model is the preclinical testing of N-acetylaspartylglutamate (NAAG) peptidase inhibitors. These compounds are selective mGluR2 agonists, which inhibit presynaptic glutamate release (377). Preclinical testing of the NAAG peptidase inhibitor, ZJ43, showed that it reduced MK-801-induced hyperlocomotion and PCP-induced stereotypic movements (378), effects due to the mGluR3 agonist action of ZJ43 (379). Interestingly, a recent report demonstrated that an mGluR2 agonist abolished LSD-induced psychotomimetic signalling and behavioural responses (200). The field awaits the results of clinical trials of this class of agents.

The most important example of predictive validity of the PCP model concerns the development of the mGluR3 agonist, LY354740, which acts to reduce release of presynaptic glutamate (380). Preclinical testing in an acute PCP-induced model demonstrated that LY354740 reduced PCP-induced stereotypic movement, hyperlocomotion, and spatial working memory deficits (281). Significantly these effects were associated with reversal of increased glutamate and dopamine effluxes prefrontally (281). Interestingly, preclinical testing of LY354740 in HVs did not significantly improve ketamine-induced psychosis ratings but it did improve ketamine-induced working memory deficits (381). Based on these results, LY354740 has been subjected to clinical trial in patients with schizophrenia. In a landmark study, acute ill patients were randomised to LY2140023 (an orally absorbable analogue of LY354740), olanzapine, or placebo. This study demonstrated that LY2140023 was effective against the positive and negative symptoms of schizophrenia and had few side-effects (382). Hence, the PCP model showed accurate predictive validity in the case of the first effective novel antipsychotic since the introduction of chlorpromazine.

The PCP model of schizophrenia: An integration

When the psychotomimetic effect of PCP was first proposed as a model of schizophrenia (383) the pharmacological actions of PCP were unknown. Although an early report hypothesised impaired function of glutamatergic neurons as a model of schizophrenia (384), it was not until the PCP binding site was localised to the NMDA receptor complex

(385) that NMDA receptor hypofunction could be incorporated into the PCP model (362, 363). A 'thalamic filter dysfunction' was proposed (362): pathological activation of the cortico-striato-thalamo-cortical feedback loop was hypothesised to cause information overload in the cortex (reviewed in 386). Strengthening evidence that the psychotomimetic effects of PCP were directly related to NMDA receptor complex antagonism challenged the highly influential dopamine hypothesis of schizophrenia (72). An important element of the PCP model, glutamatergic neuronal disinhibition due to functional antagonism of NMDA receptors on GABAergic interneurons that normally place excitatory pyramidal neurons under inhibitory control, was added more recently (387, 388). The putative role of cortical pruning (389) and evidence of reduced prefrontal neuropil (390, 391) in schizophrenia have also been incorporated into the model (361).

A number of neuropharmacological descriptions of the PCP model (hypoglutamatergic model) of schizophrenia have been published (109, 112, 332-334, 336-338, 359, 360, 392-396). Central to these models is a PCP-induced deficit of GABAergic interneurons, which results in disinhibition of glutamatergic pyramidal cells (see Figure 1, Panel A). Although this disinhibition is assumed to be widespread throughout grey matter, models emphasise its impact on prefrontal cortex in accounting for psychotomimetic effects. Increased levels of extracellular glutamate in acute PCP models are thought to result from local collateral feedback by disinhibited pyramidal neurons onto presynaptic terminals, and increased non-NMDA glutamatergic efferent feedback from thalamus, other subcortical centres, and the hippocampal formation (see Figure 1, Panel B). Completing the PCP model are descriptions of increased dopamine efflux in the prefrontal cortex and ventral pallidum, resulting from greater cortical drive to striatal/limbic subcortical centres. Increased cortical drive to the median raphe results in increased prefrontal serotonin concentrations, which augment glutamate efflux via presynaptic 5HT2A receptor activation. Importantly, ventral pallidal stimulation of the dorsomedial thalamic nucleus, and hippocampal-limbic stimulation of the anterior nucleus of the thalamus, provides an explanation for excessive subcortical-cortical glutamatergic feedback drive to the prefrontal cortex (see Figure 1, Panel B).

PLACE FIGURE 1 NEAR HERE

The acute model described above has been supplemented by a chronic PCP model, which includes reduced prefrontal extracellular glutamate and dopamine (294). A number of cellular mechanisms have been advanced to link these surface receptor-focussed models to intracellular final common pathway models. Svenningson et al. (277, 278) have implicated a common signalling pathway in the mediation of the psychotomimetic effects of glutamatergic antagonists (such as PCP), serotonergic agonists (such as LSD) and dopaminergic agonists (such as amphetamine). In this pathway, phosphorylation status of Dopamine- and an Adenosine 3',5'monophosphate (cAMP)-Regulated PhosphoProtein of 32 kilodaltons (DARPP-32) regulates downstream effector proteins, glycogen synthesis kinase-3 (GSK-3), cAMP response element-binding proteins (CREP) and c-Fos, thereby influencing electrophysiological, transcriptional, and behavioural responses. An alternative mechanism for linking the PCP model to intracellular signalling pathways is via glutamate-mediated excitotoxicity, which has been found to induce apoptotic loss of dendrites and synapses without cell body death or gliosis (reviewed in 336). Postmortem studies have reported elevated Bax:Bcl-2 ratio (a marker of increased propensity for apoptosis) in the temporal cortex (397, 398), comparable to functional findings in cultured fibroblasts from patients with schizophrenia (399). Taken together, these proposals provide a rich source of hypotheses for testing in studies into the pathogenesis of schizophrenia.

Summary and conclusion

It is concluded that although PCP, LSD and MDMA have well-documented psychotomimetic effects, only for PCP is there abundant evidence that it induced psychotic disorder beyond the acute symptoms of intoxication. In fact, there is no clear evidence that either LSD or MDMA induces psychotic disorder independent of toxication, let alone schizophrenia, in individuals who do not have vulnerability to schizophrenia premorbidly. Impressive qualitative similarity between PCP-induced symptoms and those of schizophrenia, both in range and nature, was shown by detailed examination of first-hand clinical descriptions of phenomenology. This examination was

only possible by review of primary source publications written by trained clinicians who personally observed patients and HVs experiencing PCP-related symptoms.

Although inducing quantitatively less intense psychotomimetic effects, ketamine is considered a safe and valid model of PCP psychosis, and applicable to preclinical human studies. We also concluded that rodent and primate models induced by PCP and analogues have construct validity, showing homologous behaviour, cognitive deficits, alterations in regional brain activation, and underlying neuronal dysfunction, to those observed in patients with schizophrenia. Most importantly, animal models demonstrated predictive validity at the level of hypothesis-generation about human pathophysiology and efficacy of novel drug therapies. Indeed, it could be said that PCP-related animal models have been instrumental in the discovery of the first novel class of antipsychotic drug treatments (i.e. mGluR2/3 agonists) without D2R antagonist action since the introduction of chlorpromazine. The relative merits of PCP-related and amphetamine-induced models of schizophrenia have been discussed elsewhere (3). We considered both models to have high predictive validity when descriptions and measurement are carried out at the level of neuronal dysfunction. Amphetamine-induced models highlight the importance of dosing schedules to describing models because only sensitisation induced by repeated dosing mimics schizophrenia (e.g. 253, 400-402). This issue is also relevant to PCP-related models (294). A notable limitation of neurochemical models is that they usually do not incorporate a neurodevelopmental perspective (403). This implies that developmental models will be required to complement pharmacological models (reviewed in 4), either aetiologically linked to the occurrence of schizophrenia (e.g., prenatal viral infection mimicked using poly I:C, 404), induced by a prenatal hippocampal lesion (403, 405), or based on a specific genetic alteration, exemplified by mouse models of velo-cardio-facial syndrome (406), DISC1 (407) or neuregulin-1 Type III (408).

In a more general sense this review reminds us of our field's historic dependence on research using patients. Preclinical models, especially in animals, release research from the inevitable confounding factors related to illness experience and treatment. Most

importantly animal models allow direct observation of neuronal dysfunction that models the human pathophysiology. Without this opportunity, major improvements in the drug treatment of schizophrenia will not be possible. This review also highlights the need for excellence in clinical observation and measurement in developing adequately valid animal models, which rely on the clinical insights of well-trained clinicians who are interested in the neurobiology of psychiatric disorder. Communication between the clinic and the preclinical behavioural laboratory will enable the refinement of established models and the creation of new ones (1). Insufficient well validated, objective, and reliable measures of psychopathology is a barrier to the development of homologous measurement in animal models. The validation of an animal model can only be as good as the information available in the relevant preclinical human research and the clinical literature (409). Clinical studies need to be informed by results from animal studies as much as the reverse is true. More translational science is needed to relate animal findings to humans and *vice versa (1)*.

References

1. Geyer MA, Markou A: The role of preclinical models in the development of psychotropic drugs, in Neuropsychopharmacology: The Fifth Generation of Progress. Edited by Davis KL, Charney D, Coyle JT, Nemeroff C, Lippincott Williams & Wilkins, 2002, pp 445-455
2. Robbins TW: Animal models of psychosis, in Neurobiology of Mental Illness. Edited by Charney DS, Nestler EJ. New York, Oxford University Press, 2004, pp 263-286
3. Krystal JH, Abi-Dargham A, Laruelle M, Moghaddam B: Pharmacological models of psychoses, in Neurobiology of Mental Illness. Edited by Charney DS, Nestler EJ. New York, Oxford University Press, 2004, pp 287-298
4. Carpenter WT, Koenig JI: The evolution of drug development in schizophrenia: Past issues and future opportunities. Neuropsychopharmacology 2008; online advanced copy
5. Adams CE, Rathbone J, Thornley B, Clarke M, Borrill J, Wahlbeck K, Awad AG: Chlorpromazine for schizophrenia: a Cochrane systematic review of 50 years of randomised controlled trials. BMC Medicine 2005; 3:15-21
6. Insel TR, Scolnick EM: Cure therapeutics and strategic prevention: raising the bar for mental health research. Molecular Psychiatry 2006; 11(1):11-17
7. Agid Y, Buzsaki G, Diamond DM, Frackowiak R, Giedd J, Girault JA, Grace A, Lambert JJ, Manji H, Mayberg H, Popoli M, Prochiantz A, Richter-Levin G, Somogyi P, Spedding M, Svenningsson P, Weinberger D: Viewpoint - How can drug discovery for psychiatric disorders be improved? Nature Reviews Drug Discovery 2007; 6(3):189-201
8. Sams-Dodd F: Strategies to optimize the validity of disease models in the drug discovery process. Drug Discovery Today 2006; 11(7-8):355-363
9. Mathysse S: Animal models in psychiatric research, in Progress in Brain Research, vol 65. Edited by van Ree JM, Mathysse S, Elsevier Science, 1986, pp 259-270
10. Maddox VH: The historical development of phencyclidine, in PCP (Phencyclidine): Historical and current perspectives. Edited by Domino EF. Detroit, Ann Arbor, 1981, pp 1-8
11. Johnstone M, Evans V, Baigel S: Sernyl (Cl-395) in clinical anaesthesia. British Journal of Anaesthesia 1959; 31(10):433-439
12. Cook CE, Brine DR, Jeffcoat AR, Hill JM, Wall ME, Perezreyes M, Diguiseppi SR: Phencyclidine disposition after intravenous and oral doses. Clinical Pharmacology & Therapeutics 1982; 31(5):625-634
13. Sioris LJ, Krenzelok EP: Phencyclidine Intoxication – Literature Review. American Journal of Hospital Pharmacy 1978; 35(11):1362-1367
14. Griefenstein FE, Yoshitake J, Devault M, Gajewski JE: A study of a 1-Aryl cyclo hexyl amine for anesthesia. Anesthesia & Analgesia 1958; 37(5):283-294
15. Collins VJ, Gorospe CA, Rovenstine EA: Intravenous nonbarbiturate, nonnarcotic analgesics: Preliminary studies. Cyclohexylamines. Anesthesia & Analgesia 1960; 39:302-306

16. Burns RS, Lerner SE: The effects of phencyclidine in man: A review, in PCP (Phencyclidine): Historical and current perspectives. Edited by Domino EF. Detroit, Ann Arbor, 1981, pp 449-470
17. Zukin SR, Lowinson JH, Zylberman I: Substance abuse: Phencyclidine use disorder, in Psychiatry, Volume 1. Edited by Tasman A, Kay J, Lieberman JA. West Sussex, John Wiley & Sons, 2004, pp 1010-1045
18. Walberg CB, McCarron MM, Schlulze BW: Quantitation of phencyclidine in serum by enzyme immunoassay: Results in 405 patients. Journal of Analytical Toxicology 1983; 7:106-110
19. Meyer JS, Greifenstein F, Devault M: A new drug causing symptoms of sensory deprivation - neurological, electroencephalographic and pharmalogical effects of Sernyl. Journal of Nervous and Mental Disease 1959; 129(1):54-61
20. Kothary SP, Zsigmond EK: A double-blind study of the effective antihallucinatory doses of diazepam prior to ketamine anesthesia. Clinical Pharmacology and Therapeutics 1977; 21:108-109
21. Helrich M, Atwood JM: Modification of Sernyl anesthesia with haloperidol. Anesthesia and Aanalgesia 1964; 43(5):471-474
22. Petersen RC, Stillman RC: Phencyclidine: An overview, in Phencyclidine (PCP) Abuse: An Appraisal, Monograph 21. Edited by Petersen RC, Stillman RC. Rockville, Maryland, National Institute on Drug Abuse, 1978, pp 1-17
23. Newmeyer JA: The epidemiology of PCP use in the late 1970s. Journal of Psychedelic Drugs 1980; 12(3-4):211-215
24. Stillman R, Petersen RC: Paradox of phencyclidine (PCP) abuse. Annals of Internal Medicine 1979; 90(3):428-430
25. Siegel RK: Phencyclidine and ketamine intoxication: A study of four populations of recreational users, in Phencyclidine (PCP) Abuse: An Appraisal, Monograph 21. Edited by Petersen RC, Stillman RC. Rockville, Maryland, National Institute on Drug Abuse, 1978, pp 119-147
26. Aniline O, Allen RE, Pitts FN, Yago LS, Pitts AF: The urban epidemic of phencyclidine use - laboratory evidence from a public psychiatric hospital inpatient service. Biological Psychiatry 1980; 15(5):813-817
27. Fauman B, Baker F, Coppleson LW, Rosen P, Segal MB: Psychosis induced by phencyclidine. Concepts, Components and Configurations 1975; 4(3):223-225
28. Fauman MA, Fauman B: The psychiatric aspects of chronic phencyclidine use: A study of chronic PCP users, in Phencyclidine (PCP) Abuse: An Appraisal, Monograph 21. Edited by Petersen RC, Stillman RC. Rockville, Maryland, National Institute on Drug Abuse, 1978, pp 183-200
29. Luisada PV: The phencyclidine psychosis: Phenomenology and treatment, in Phencyclidine (PCP) Abuse: An Appraisal, Monograph 21. Edited by Petersen RC, Stillman RC. Rockville, Maryland, National Institute on Drug Abuse, 1978, pp 241-253
30. Smith DE, Wesson DR, Buxton ME, Seymour R, Kramer HM: The diagnosis and treatment of the PCP abuse syndrome, in Phencyclidine (PCP) Abuse: An Appraisal, Monograph 21. Edited by Petersen RC, Stillman RC. Rockville, Maryland, National Institute on Drug Abuse, 1978, pp 229-240

31. Erard R, Luisada PV, Peele R: The PCP psychosis - prolonged intoxication or drug precipitated functional illness. Journal of Psychedelic Drugs 1980; 12(3-4):235-251
32. Yago KB, Pitts FN, Burgoyne RW, Aniline O, Yago LS, Pitts AF: The urban epidemic of phencyclidine (PCP) use - Clinical and laboratory evidence from a public psychiatric hospital emergency service. Journal of Clinical Psychiatry 1981; 42(5):193-196
33. Yesavage JA, Freman AM: Acute phencyclidine (PCP) intoxication - Psychopathology and prognosis. Journal of Clinical Psychiatry 1978; 39(8):664-666
34. Allen RM, Young SJ: Phencyclidine-induced psychosis. American Journal of Psychiatry 1978; 135(9):1081-1084
35. Gwirtsman HE, Wittkop W, Gorelick D, Lemberg A, Motis G: Phencyclidine intoxication - Incidence, clinical patterns and course of treatment. Research Communications in Psychology Psychiatry and Behavior 1984; 9(4):405-410
36. McCarron MM, Schulze BW, Thompson GA, Conder MC, Goetz WA: Acute phencyclidine intoxication - Incidence of clinical findings in 1,000 cases. Annals of Emergency Medicine 1981; 10(5):237-242
37. Luisada PV, Brown BI: Clinical management of phencyclidine psychosis. Clinical Toxicology 1976; 9(4):539-545
38. Pearlson GD: Psychiatric and medical syndromes associated with phencyclidine (PCP) abuse. Johns Hopkins Medical Journal 1981; 148(1):25-33
39. Wright HH, Cole EA, Batey SR, Hanna K: Phencyclidine-induced psychosis - 8-year follow-up of 10 cases. Southern Medical Journal 1988; 81(5):565-567
40. Burns RS, Lerner SE: Perspectives - Acute phencyclidine intoxication. Clinical Toxicology 1976; 9(4):477-501
41. Rainey JM, Crowder MK: Prevalence of phencyclidine in street drug preparations. New England Journal of Medicine 1974; 290(8):466-467
42. Giannini AJ, Eighan MS, Loiselle RH, Giannini MC: Comparison of haloperidol and chlorpromazine in the treatment of phencyclidine psychosis. Journal of Clinical Pharmacology 1984; 24(4):202-204
43. Lerner SE, Burns RS: Phencyclidine use among youth: History, epidemiology, and acute and chronic intoxication, in Phencyclidine (PCP) Abuse: An Appraisal, Monograph 21. Edited by Petersen RC, Stillman RC. Rockville, Maryland, National Institute on Drug Abuse, 1978, pp 66-118
44. Kay J, Tasman A: Essentials of Psychiatry. West Sussex, John Wiley and Sons, 2006
45. Liden CB, Lovejoy FH, Costello CE: Phencyclidine - 9 Cases of poisoning. JAMA Journal of the American Medical Association 1975; 234(5):513-516
46. Burns RS, Lerner SE, Corrado R, James SH, Schnoll SH: Phencyclidine - States of acute intoxication and fatalities. Western Journal of Medicine 1975; 123(5):345-349
47. Fauman MA, Fauman BJ: The differential diagnosis of organic based psychiatric disturbance in the emergency department. Concepts, Components and Configurations 1977; 6(7):315-323

48. Smith DE: A clinical approach to the treatment of PCP abuse, in PCP (phencyclidine): Historical and current perspectives. Edited by Domino EF. Detroit, Ann Arbor, 1981, pp 471-486
49. Domino EF, Luby ED: Abnormal mental states induced by phencyclidine as a model of schizophrenia, in PCP (phencyclidine): Historical and current perspectives. Edited by Domino EF. Detroit, Ann Arbor, 1981, pp 401-419
50. Ban TA, Lohrenz JJ, Lehmann HE: Observations on the action of sernyl - a new psychotropic drug. Canadian Psychiatric Association Journal 1961; 6(3):150-157
51. Rosse RB, Collins JP, Faymccarthy M, Alim TN, Wyatt RJ, Deutsch SI: Phenomenological comparison of the idiopathic psychosis of schizophrenia and drug-induced cocaine and phencyclidine psychoses - a retrospective study. Clinical Neuropharmacology 1994; 17(4):359-369
52. Davies BM, Beech HR: The effect of 1-arylcyclohexylamine (Sernyl) on 12 normal volunteers. Journal of Mental Science 1960; 106(444):912-924
53. Rosenbaum G, Cohen BD, Luby ED, Gottlieb JS, Yelen D: Comparison of Sernyl with other drugs - simulation of schizophrenic performance with Sernyl, LSD-25, and amobarbital (Amytal) sodium. 1. Attention, motor function, and proprioception. Archives of General Psychiatry 1959; 1(6):651-656
54. Carls KA, Ruehter VL: An evaluation of phencyclidine (PCP) psychosis: A retrospective analysis at a state facility. American Journal of Drug and Alcohol Abuse 2006; 32(4):673-678
55. Giannini AJ, Nageotte C, Loiselle RH, Malone DA, Price WA: Comparison of chlorpromazine, haloperidol and pimozide in the treatment of phencyclidine psychosis - D2 receptor specificity. Journal of Toxicology - Clinical Toxicology 1984; 22(6):573-579
56. Luby ED, Cohen BD, Rosenbaum G, Gottlieb JS, Kelley R: Study of a new schizophrenomimetic drug - Sernyl. Archives of Neurology and Psychiatry 1959; 81(3):363-369
57. Levy L, Cameron DE, Aitken RCB: Observation on 2 psychotomimetic drugs of piperidine derivation-Ci-395 (Sernyl) and Ci-400. American Journal of Psychiatry 1960; 116(9):843-844
58. Itil T, Keskiner A, Kiremitci N, Holden JMC: Effect of phencyclidine in chronic schizophrenics. Canadian Psychiatric Association Journal 1967; 12(2):209-212
59. Cohen BD, Rosenbaum G, Gottlieb JS, Luby ED: Comparison of phencyclidine hydrochloride (Sernyl) with other drugs - Simulation of schizophrenic performance with phencyclidine hydrochloride (Sernyl), lysergic-acid diethylamide (LSD-25), and amobarbital (Amytal) sodium. 2. Symbolic and sequential thinking. Archives of General Psychiatry 1962; 6(5):395-401
60. Bakker CB, Amini FB: Observations on the psychotomimetic effects of Sernyl. Comprehensive Psychiatry 1961; 2:269-280
61. Braff DL, Geyer MA, Swerdlow NR: Human studies of prepulse inhibition of startle: normal subjects, patient groups, and pharmacological studies. Psychopharmacology 2001; 156(2-3):234-258
62. Domino EF, Chodoff P, Corssen G: Pharmacologic effects of Cl-581 a new dissociative anesthetic in man. Clinical Pharmacology & Therapeutics 1965; 6(3):279-291

63. Wolff K, Winstock AR: Ketamine - From medicine to misuse. CNS Drugs 2006; 20(3):199-218
64. White PF, Way WL, Trevor AJ: Ketamine - Its pharmacology and therapeutic uses. Anesthesiology 1982; 56(2):119-136
65. Idvall J, Ahlgren I, Aronsen KF, Stenberg P: Ketamine infusions - Pharmacokinetics and clinical effects. British Journal of Anaesthesia 1979; 51(12):1167-1173
66. Bennett JA, Bullimore JA: Use of ketamine hydrochloride anesthesia for radiotherapy in young children. British Journal of Anaesthesia 1973; 45(2):197-201
67. Slogoff S, Allen GW, Wessels JV, Cheney DH: Clinical experience with subanesthetic ketamine. Anesthesia and Analgesia 1974; 53(3):354-358
68. White JM, Ryan CF: Pharmacological properties of ketamine. Drug and Alcohol Review 1996; 15(2):145-155
69. Reier CE: Ketamine - Dissociative agent or hallucinogen? New England Journal of Medicine 1971; 284(14):791-792
70. Collier BB: Ketamine and conscious mind. Anaesthesia 1972; 27(2):120-134
71. Modvig KM, Nielsen SF: Psychological changes in children after anesthesia - Comparison between halothane and ketamine. Acta Anaesthesiologica Scandinavica 1977; 21(6):541-544
72. Javitt DC, Zukin SR: Recent advances in the phencyclidine model of schizophrenia. American Journal of Psychiatry 1991; 148(10):1301-1308
73. Vincent JP, Kartalovski B, Geneste P, Kamenka JM, Lazdunski M: Interaction of phencyclidine (angel dust) with a specific receptor in rat brain membranes. Proceedings of the National Academy of Sciences of the United States of America 1979; 76(9):4678-4682
74. Hampton RY, Medzihradsky F, Woods JH, Dahlstrom PJ: Stereospecific binding of H-3-labeled phencyclidine in brain membranes. Life Sciences 1982; 30(25):2147-2154
75. FDA Drug Bulletin: Ketamine abuse. FDA Drug Bulletin 1979; 9(4):24
76. Dotson JW, Ackerman DL, West LJ: Ketamine abuse. Journal of Drug Issues 1995; 25(4):751-757
77. Jansen KLR: A review of the nonmedical use of ketamine: Use, users and consequences. Journal of Psychoactive Drugs 2000; 32(4):419-433
78. Stafford P: Psychedelics Encyclopedia. Berkeley, California, Ronin Publishing, 1992
79. Lankenau SE, Clatts MC: Ketamine injection among high risk youth: Preliminary findings from New York City. Journal of Drug Issues 2002; 32(3):893-905
80. Maxwell JC: Party drugs: Properties, prevalence, patterns, and problems. Substance Use & Misuse 2005; 40(9-10):1203-1240
81. Maxwell JC: The response to club drug use. Current Opinion in Psychiatry 2003; 16(3):279-289
82. Lyttle T, Montagne M: Drugs, music, and ideology - a social pharmacological interpretation of the acid house movement. International Journal of the Addictions 1992; 27(10):1159-1177

83. Degenhardt L, Copeland J, Dillon P: Recent trends in the use of "club drugs": An Australian review. Substance Use & Misuse 2005; 40(9-10):1241-1256
84. Weiner AL, Vieira L, McKay CA, Bayer MJ: Ketamine abusers presenting to the emergency department: A case series. Journal of Emergency Medicine 2000; 18(4):447-451
85. Lim DK: Ketamine associated psychedelic effects and dependence. Singapore Medical Journal 2003; 44(1):31-34
86. Dillon P, Copeland J, Jansen K: Patterns of use and harms associated with non-medical ketamine use. Drug and Alcohol Dependence 2003; 69(1):23-28
87. Uhlhaas PJ, Millard I, Muetzelfeldt L, Curran HV, Morgan CJA: Perceptual organization in ketamine users: preliminary evidence of deficits on night of drug use but not 3 days later. Journal of Psychopharmacology 2007; 21(3):347-352
88. Curran HV, Monaghan L: In and out of the K-hole: a comparison of the acute and residual effects of ketamine in frequent and infrequent ketamine users. Addiction 2001; 96(5):749-760
89. Curran HV, Morgan C: Cognitive, dissociative and psychotogenic effects of ketamine in recreational users on the night of drug use and 3 days later. Addiction 2000; 95(4):575-590
90. Morgan CJA, Riccelli M, Maitland CH, Curran HV: Long-term effects of ketamine: evidence for a persisting impairment of source memory in recreational users. Drug and Alcohol Dependence 2004; 75(3):301-308
91. Carpenter WT: The schizophrenia ketamine challenge study debate. Biological Psychiatry 1999; 46(8):1081-1091
92. Kudoh A, Katagai H, Takazawa T: Anesthesia with ketamine, propofol, and fentanyl decreases the frequency of postoperative psychosis emergence and confusion in schizophrenic patients. Journal of Clinical Anesthesia 2002; 14(2):107-110
93. Lahti AC, Holcomb HH, Medoff DR, Tamminga CA: Ketamine Activates Psychosis and Alters Limbic Blood-Flow in Schizophrenia. Neuroreport 1995; 6(6):869-872
94. Malhotra AK, Pinals DA, Adler CM, Elman I, Clifton A, Pickar D, Breier A: Ketamine-induced exacerbation of psychotic symptoms and cognitive impairment in neuroleptic-free schizophrenics. Neuropsychopharmacology 1997; 17(3):141-150
95. Malhotra AK, Adler CM, Kennison SD, Elman I, Pickar D, Breier A: Clozapine blunts N-methyl-D-aspartate antagonist-induced psychosis: A study with ketamine. Biological Psychiatry 1997; 42(8):664-668
96. Lahti AC, Weiler MA, Michaelidis T, Parwani A, Tamminga CA: Effects of ketamine in normal and schizophrenic volunteers. Neuropsychopharmacology 2001; 25(4):455-467
97. Pomarol-Clotet E, Honey GD, Murray GK, Corlett PR, Absalom AR, Lee M, McKenna PJ, Bullmore ET, Fletcher PC: Psychological effects of ketamine in healthy volunteers - Phenomenological study. British Journal of Psychiatry 2006; 189:173-179

98. Ghoneim MM, Hinrichs JV, Mewaldt SP, Petersen RC: Ketamine - Behavioral-effects of subanesthetic doses. Journal of Clinical Psychopharmacology 1985; 5(2):70-77
99. Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, Heninger GR, Bowers MB, Charney DS: Subanesthetic effects of the non-competitive NMDA antagonist, ketamine, in humans - Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Archives of General Psychiatry 1994; 51(3):199-214
100. Adler CM, Goldberg TE, Malhotra AK, Pickar D, Breier A: Effects of ketamine on thought disorder, working memory, and semantic memory in healthy volunteers. Biological Psychiatry 1998; 43(11):811-816
101. Adler CM, Malhotra AK, Elman I, Goldberg T, Egan M, Pickar D, Breier A: Comparison of ketamine-induced thought disorder in healthy volunteers and thought disorder in schizophrenia. American Journal of Psychiatry 1999; 156(10):1646-1649
102. Covington MA, Riedel WJ, Brown C, He CZ, Morris E, Weinstein S, Semple J, Brown J: Does ketamine mimic aspects of schizophrenic speech? Journal of Psychopharmacology 2007; 21(3):338-346
103. Malhotra AK, Pinals DA, Weingartner H, Sirocco K, Missar CD, Pickar D, Breier A: NMDA receptor function and human cognition: The effects of ketamine in healthy volunteers. Neuropsychopharmacology 1996; 14(5):301-307
104. Krystal JH, Perry EB, Gueorguieva R, Belger A, Madonich SH, Abi-Dargham A, Cooper TB, MacDougall L, Abi-Saab W, D'Souza DC: Comparative and interactive human psychopharmacologic effects of ketamine and amphetamine - Implications for glutamatergic and dopaminergic model psychoses and cognitive function. Archives of General Psychiatry 2005; 62(9):985-995
105. Gouzoulis-Mayfrank E, Heekeren K, Neukirch A, Stoll M, Stock C, Obradovic M, Kovar KA: Psychological effects of (S)-ketamine and N,N-dimethyltryptamine (DMT): A double-blind, cross-over study in healthy volunteers. Pharmacopsychiatry 2005; 38(6):301-311
106. Vollenweider FX, Leenders KL, Oye I, Hell D, Angst J: Differential psychopathology and patterns of cerebral glucose utilisation produced by (S)- and (R)-ketamine in healthy volunteers using positron emission tomography (PET). European Neuropsychopharmacology 1997; 7(1):25-38
107. Newcomer JW, Farber NB, Jevtovic-Todorovic V, Selke G, Melson AK, Hershey T, Craft S, Olney JW: Ketamine-induced NMDA receptor hypofunction as a model of memory impairment and psychosis. Neuropsychopharmacology 1999; 20(2):106-118
108. Morgan CJA, Curran HV: Acute and chronic effects of ketamine upon human memory: a review. Psychopharmacology 2006; 188(4):408-424
109. Krystal JH, D'Souza DC, Mathalon D, Perry E, Belger A, Hoffman R: NMDA receptor antagonist effects, cortical glutamatergic function, and schizophrenia: toward a paradigm shift in medication development. Psychopharmacology 2003; 169(3-4):215-233

110. McFarland NR, Haber SN: Thalamic relay nuclei of the basal ganglia form both reciprocal and nonreciprocal cortical connections, linking multiple frontal cortical areas. Journal of Neuroscience 2002; 22(18):8117-8132
111. Pantelis C, Barnes TRE, Nelson HE, Tanner S, Weatherley L, Owen AM, Robbins TW: Frontal-striatal cognitive deficits in patients with chronic schizophrenia. Brain 1997; 120:1823-1843
112. Sharp FR, Tomitaka M, Bernaudin M, Tomitaka S: Psychosis: pathological activation of limbic thalamocortical circuits by psychomimetics and schizophrenia? Trends in Neurosciences 2001; 24(6):330-334
113. Harborne GC, Watson FL, Healy DT, Groves L: The effects of sub-anaesthetic doses of ketamine on memory, cognitive performance and subjective experience in healthy volunteers. Journal of Psychopharmacology 1996; 10(2):134-140
114. Radant AD, Bowdle TA, Cowley DS, Kharasch ED, Roy-Byrne PP: Does ketamine-mediated N-methyl-D-aspartate receptor antagonism cause schizophrenia-like oculomotor abnormalities? Neuropsychopharmacology 1998; 19(5):434-444
115. Krystal JH, D'Souza DC, Karper LP, Bennett A, Abi-Dargham A, Abi-Saab D, Cassello K, Bowers MB, Vegso S, Heninger GR, Charney DS: Interactive effects of subanesthetic ketamine and haloperidol in healthy humans. Psychopharmacology 1999; 145(2):193-204
116. Krystal JH, Karper LP, Bennett A, D'Souza DC, Abi-Dargham A, Morrissey K, Abi-Saab D, Bremner JD, Bowers MB, Suckow RF, Stetson P, Heninger GR, Charney DS: Interactive effects of subanesthetic ketamine and subhypnotic lorazepam in humans. Psychopharmacology 1998; 135(3):213-229
117. Parwani A, Weiler MA, Blaxton TA, Warfel D, Hardin M, Frey K, Lahti AC: The effects of a subanesthetic dose of ketamine on verbal memory in normal volunteers. Psychopharmacology 2005; 183(3):265-274
118. LaPorte DJ, Blaxton TA, Michaelidis T, Robertson DU, Weiler MA, Tamminga CA, Lahti AC: Subtle effects of ketamine on memory when administered following stimulus presentation. Psychopharmacology 2005; 180(3):385-390
119. Morgan CJA, Mofeez A, Brandner B, Bromley L, Curran HV: Ketamine impairs response inhibition and is positively reinforcing in healthy volunteers: a dose-response study. Psychopharmacology 2004; 172(3):298-308
120. Hetem LAB, Danion JM, Diemunsch P, Brandt C: Effect of a subanesthetic dose of ketamine on memory and conscious awareness in healthy volunteers. Psychopharmacology 2000; 152(3):283-288
121. Lofwall MR, Griffiths RR, Mintzer MZ: Cognitive and subjective acute dose effects of intramuscular ketamine in healthy adults. Experimental and Clinical Psychopharmacology 2006; 14(4):439-449
122. Honey GD, O'Loughlin C, Turner DC, Pomarol-Clotet E, Corlett PR, Fletcher PC: The effects of a subpsychotic dose of ketamine on recognition and source memory for agency: Implications for pharmacological modelling of core symptoms of schizophrenia. Neuropsychopharmacology 2006; 31(2):413-423
123. Fletcher PC, Honey GD: Schizophrenia, ketamine and cannabis: Evidence of overlapping memory deficits. Trends in Cognitive Sciences 2006; 10(4):167-174

124. Honey RAE, Turner DC, Honey GD, Sharar SR, Kumaran D, Pomarol-Clotet E, McKenna P, Sahakian B, Robbins TW, Fletcher P: Subdissociative dose ketamine produces a deficit in manipulation but not maintenance of the contents of working memory. Neuropsychopharmacology 2003; 28(11):2037-2044
125. Passie T, Karst M, Wiese B, Emrich HM, Schneider U: Effects of different subanesthetic doses of (S)-ketamine on neuropsychology, psychopathology, and state of consciousness in man. Neuropsychobiology 2005; 51(4):226-233
126. Gouzoulis-Mayfrank E, Heekeren K, Neukirch A, Stoll M, Stock C, Daumann J, Obradovic M, Kovar KA: Inhibition of return in the human 5HT(2A) agonist and NMDA antagonist model of psychosis. Neuropsychopharmacology 2006; 31(2):431-441
127. Abel KM, Allin MPG, Hemsley DR, Geyer MA: Low dose ketamine increases prepulse inhibition in healthy men. Neuropharmacology 2003; 44(6):729-737
128. Krystal JH, Bennett A, Abi-Saab D, Belger A, Karper LP, D'Souza DC, Lipschitz D, Abi-Dargham A, Charney DS: Dissociation of ketamine effects on rule acquisition and rule implementation: Possible relevance to NMDA receptor contributions to executive cognitive functions. Biological Psychiatry 2000; 47(2):137-143
129. Morgan CJA, Mofeez A, Brandner B, Bromley L, Curran HV: Acute effects of ketamine on memory systems and psychotic symptoms in healthy volunteers. Neuropsychopharmacology 2004; 29(1):208-218
130. Fletcher PC, Henson RNA: Frontal lobes and human memory - Insights from functional neuroimaging. Brain 2001; 124:849-881
131. Henson R: A mini-review of fMRI studies of human medial temporal lobe activity associated with recognition memory. Quarterly Journal of Experimental Psychology Section B-Comparative and Physiological Psychology 2005; 58(3-4):340-360
132. Ragland JD, Gur RC, Valdez J, Turetsky BI, Elliott M, Kohler C, Siegel S, Kanes S, Gur RE: Event-related fMRI of frontotemporal activity during word encoding and recognition in schizophrenia. American Journal of Psychiatry 2004; 161(6):1004-1015
133. Hofer A, Weiss EM, Golaszewski SM, Siedentopf CM, Brinkhoff C, Kremser C, Felber S, Fleischhacker WW: Neural correlates of episodic encoding and recognition of words in unmedicated patients during an acute episode of schizophrenia: A functional MRI study. American Journal of Psychiatry 2003; 160(10):1802-1808
134. Glahn DC, Ragland JD, Abramoff A, Barrett J, Laird AR, Bearden CE, Velligan DI: Beyond hypofrontality: A quantitative meta-analysis of functional neuroimaging studies of working memory in schizophrenia. Human Brain Mapping 2005; 25(1):60-69
135. Ragland JD, Gur RC, Raz J, Schroeder L, Kohler CG, Smith RJ, Alavi A, Gur RE: Effect of schizophrenia on frontotemporal activity during word encoding and recognition: A PET cerebral blood flow study. American Journal of Psychiatry 2001; 158(7):1114-1125
136. Tamminga CA, Thaker GK, Buchanan R, Kirkpatrick B, Alphs LD, Chase TN, Carpenter WT: Limbic system abnormalities identified in schizophrenia using

positron emission tomography with fluorodeoxyglucose and neocortical alterations with deficit syndrome. Archives of General Psychiatry 1992; 49(7):522-530

137. Andreasen NC, Oleary DS, Cizadlo T, Arndt S, Rezai K, Ponto LLB, Watkins GL, Hichwa RD: Schizophrenia and cognitive dysmetria: A positron-emission tomography study of dysfunctional prefrontal-thalamic-cerebellar circuitry. Proceedings of the National Academy of Sciences of the United States of America 1996; 93(18):9985-9990
138. Andreasen NC, Rezai K, Alliger R, Swayze VW, Flaum M, Kirchner P, Cohen G, Oleary DS: Hypofrontality in neuroleptic-naive patients and in patients with chronic schizophrenia - Assessment with Xe-133 single photon emission computed tomography and the Tower of London. Archives of General Psychiatry 1992; 49(12):943-958
139. Haznedar MM, Buchsbaum MS, Luu C, Hazlett EA, Siegel BV, Lohr J, Wu J, Haier RJ, Bunney WE: Decreased anterior cingulate gyrus metabolic rate in schizophrenia. American Journal of Psychiatry 1997; 154(5):682-684
140. Siegel BV, Buchsbaum MS, Bunney WE, Gottschalk LA, Haier RJ, Lohr JB, Lottenberg S, Najafi A, Nuechterlein KH, Potkin SG, Wu JC: Cortical-striatal-thalamic circuits and brain glucose metabolic activity in 70 unmedicated male-schizophrenic patients. American Journal of Psychiatry 1993; 150(9):1325-1336
141. Jessen F, Scheef L, Germeshausen L, Tawo Y, Kockler M, Kuhn KU, Maier W, Schild HH, Heun R: Reduced hippocampal activation during encoding and recognition of words in schizophrenia patients. American Journal of Psychiatry 2003; 160(7):1305-1312
142. Holcomb HH, Lahti AC, Medoff DR, Cullen T, Tamminga CA: Effects of noncompetitive NMDA receptor blockade on anterior cingulate cerebral blood flow in volunteers with schizophrenia. Neuropsychopharmacology 2005; 30(12):2275-2282
143. Honey GD, Honey RAE, O'Loughlin C, Sharar SR, Kumaran D, Suckling J, Menon DK, Sleator C, Bullmore ET, Fletcher PC: Ketamine disrupts frontal and hippocampal contribution to encoding and retrieval of episodic memory: An fMRI study. Cerebral Cortex 2005; 15(6):749-759
144. Honey RAE, Honey GD, O'Loughlin C, Sharar SR, Kumaran D, Bullmore ET, Menon DK, Donovan T, Lupson VC, Bisbrown-Chippendale R, Fletcher PC: Acute ketamine administration alters the brain responses to executive demands in a verbal working memory task: an fMRI study. Neuropsychopharmacology 2004; 29(6):1203-1214
145. Fu CHY, Abel KM, Allin MPG, Gasston D, Costafreda SG, Suckling J, Williams SCR, McGuire PK: Effects of ketamine on prefrontal and striatal regions in an overt verbal fluency task: a functional magnetic resonance imaging study. Psychopharmacology 2005; 183(1):92-102
146. Langsjo JW, Salmi E, Kaisti KK, Aalto S, Hinkka S, Aantaa R, Oikonen V, Viljanen T, Kurki T, Silvanto M, Scheinin H: Effects of subanesthetic ketamine on regional cerebral glucose metabolism in humans. Anesthesiology 2004; 100(5):1065-1071

147. Langsjo JW, Kaisti KK, Aalto S, Hinkka S, Aantaa R, Oikonen V, Sipila H, Kurki T, Silvanto M, Scheinin H: Effects of subanesthetic doses of ketamine on regional cerebral blood flow, oxygen consumption, and blood volume in humans. Anesthesiology 2003; 99(3):614-623
148. Stone JM, Erlandsson K, Arstad E, Bressan RA, Squassante L, Teneggi V, Ell PJ, Pilowsky LS: Ketamine displaces the novel NMDA receptor SPET probe [I-123]CNS-1261 in humans in vivo. Nuclear Medicine and Biology 2006; 33(2):239-243
149. van Berckel BNM, Oranje B, van Ree JM, Verbaten MN, Kahn RS: The effects of low dose ketamine on sensory gating, neuroendocrine secretion and behavior in healthy human subjects. Psychopharmacology 1998; 137(3):271-281
150. Oranje B, Gispen-de Wied CC, Verbaten MN, Kahn RS: Modulating sensory gating in healthy volunteers: The effects of ketamine and haloperidol. Biological Psychiatry 2002; 52(9):887-895
151. Heekeren K, Neukirch A, Daumann J, Stoll M, Obradovic M, Kovar KA, Geyer MA, Gouzoulis-Mayfrank E: Prepulse inhibition of the startle reflex and its attentional modulation in the human S-ketamine and N,N-dimethyltryptamine (DMT) models of psychosis. Journal of Psychopharmacology 2007; 21(3):312-320
152. Duncan EJ, Madonick SH, Parwani A, Angrist B, Rajan R, Chakravorty S, Efferen TR, Szilagyi S, Stephanides M, Chappell PB, Gonzenbach S, Ko GN, Rotrosen JP: Clinical and sensorimotor gating effects of ketamine in normals. Neuropsychopharmacology 2001; 25(1):72-83
153. Umbricht D, Schmid L, Koller R, Vollenweider FX, Hell D, Javitt DC: Ketamine-induced deficits in auditory and visual context-dependent processing in healthy volunteers - Implications for models of cognitive deficits in schizophrenia. Archives of General Psychiatry 2000; 57(12):1139-1147
154. Sauer H, Kreitschmann-Andermahr I, Gaser E, Nowak H, Demme U, Rosburg T: Ketamine reduces the neuromagnetic mismatch reaction. Schizophrenia Research 2000; 41(1):148-148
155. O'Brien R, Cohen S: Encyclopedia of drug abuse. New York, Facts on File, 1984
156. Aghajanian GK, Marek GJ: Serotonin model of schizophrenia: emerging role of glutamate mechanisms. Brain Research Reviews 2000; 31(2-3):302-312
157. Henderson LA, Glass WJ: LSD: Still with us after all these years. San Francisco, Jossey-Bass Publishers, 1998
158. Grinspoon L, Bakalar JB: Psychedelic drugs reconsidered. New York, The Lindesmith Center, 1998
159. Houston J: Phenomenology of the psychedelic experience, in Psychodelic Drugs. Edited by Hicks RE, Fink PJ. New York, Grune & Stratton, 1969, pp 1-7
160. Katz MM, Waskow IE, Olsson J: Characterizing Psychological State Produced by LSD. Journal of Abnormal Psychology 1968; 73(1):1-14
161. Stone AL, O'Brien MS, De la Torre A, Anthony JC: Who is becoming hallucinogen dependent soon after hallucinogen use starts? Drug and Alcohol Dependence 2007; 87(2-3):153-163
162. Siegel RK, West LJ: Hallucinations. Behavior, experience & theory. New York, John Wiley & Sons, 1975

163. Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE: Monitoring the Future. National results on adolescent drug use. Overview of key findings, 2005. Bethesda, MD, National Institute on Drug Abuse, 2006
164. Riley SCE, James C, Gregory D, Dingle H, Cadger M: Patterns of recreational drug use at dance events in Edinburgh, Scotland. Addiction 2001; 96(7):1035-1047
165. Lenton S, Boys A, Norcross K: Raves, drugs and experience: drug use by a sample of people who attend raves in Western Australia. Addiction 1997; 92(10):1327-1337
166. McCambridge J, Winstock A, Hunt N, Mitcheson L: 5-year trends in use of hallucinogens and other adjunct drugs among UK dance drug users. European Addiction Research 2007; 13(1):57-64
167. Halpern JH: The use of hallucinogens in the treatment of addiction. Addiction Research 1996; 4(2):177-189
168. Cohen S: Lysergic acid diethylamide - Side-effects and complications. Journal of Nervous and Mental Disease 1960; 130(1):30-40
169. Levine J, Ludwig AM: The LSD controversy. Comprehensive Psychiatry 1964; 5(5):314-321
170. Cohen S, Ditman KS: Prolonged adverse reactions to lysergic acid diethylamide. Archives of General Psychiatry 1963; 8(5):475-480
171. Cholden LS, Kurland A, Savage C: Clinical reactions and tolerance to LSD in chronic schizophrenia. Journal of Nervous and Mental Disease 1955; 122(3):211-221
172. Fink M, Simeon J, Haque W, Itil T: Prolonged adverse reactions to LSD in psychotic subjects. Archives of General Psychiatry 1966; 15(5):450-454
173. Abraham HD, Aldridge AM: Adverse consequences of lysergic acid diethylamide. Addiction 1993; 88(10):1327-1334
174. Strassman RJ: Adverse reactions to psychedelic drugs - a review of the literature. Journal of Nervous and Mental Disease 1984; 172(10):577-595
175. Abraham HD, Aldridge AM, Gogia P: The psychopharmacology of hallucinogens. Neuropsychopharmacology 1996; 14(4):285-298
176. Glass GS, Bowers MB: Chronic psychosis associated with long-term psychotomimetic drug abuse. Archives of General Psychiatry 1970; 23(2):97-103
177. Hays P, Tilley JR: Differences between LSD psychosis and schizophrenia. Canadian Psychiatric Association Journal 1973; 18(4):331-333
178. Sedman G, Kenna JC: The use of LSD-25 as a diagnostic aid in doubtful cases of schizophrenia. British Journal of Psychiatry 1965; 111(470):96-100
179. Vardy MM, Kay SR: LSD psychosis or LSD induced schizophrenia - A multimethod inquiry. Archives of General Psychiatry 1983; 40(8):877-883
180. Ungerlei.Jt, Fisher DD, Fuller M: Dangers of LSD - Analysis of 7 months experience in a university hospitals psychiatric service. Journal of the American Medical Association 1966; 197(6):389-392
181. Frosch WA, Robbins ES, Stern M: Untoward reactions to lysergic acid diethylamide (LSD) resulting in hospitalization. New England Journal of Medicine 1965; 273(23):1235-1239

182. Bowers MB, Swigar ME: Vulnerability to psychosis associated with hallucinogen use. Psychiatry Research 1983; 9(2):91-97
183. Potvin S, Stip E, Roy J-Y: Toxic psychoses as pharmacological models of schizophrenia. Current Psychiatry Review 2005; 1:23-32
184. Langs RJ, Barr HL: Lysergic acid diethylamide (LSD-25) and schizophrenic reactions - A comparative study. Journal of Nervous and Mental Disease 1968; 147(2):163-172
185. Hollister LE: Clinical syndrome from LSD-25 compared with epinephrine. Diseases of the Nervous System 1964; 25(7):427-429
186. Breier A: Serotonin, Schizophrenia and antipsychotic drug action. Schizophrenia Research 1995; 14(3):187-202
187. Riba J, Rodriguez-Fornells A, Barbanoj MJ: Effects of ayahuasca on sensory and sensorimotor gating in humans as measured by P50 suppression and prepulse inhibition of the startle reflex, respectively. Psychopharmacology 2002; 165(1):18-28
188. Gouzoulis-Mayfrank E, Heekeren K, Thelen B, Lindenblatt H, Kovar KA, Sass H, Geyer MA: Effects of the hallucinogen psilocybin on habituation and prepulse inhibition of the startle reflex in humans. Behavioural Pharmacology 1998; 9(7):561-566
189. Umbricht D, Koller R, Vollenweider FX, Schmid L: Mismatch negativity predicts psychotic experiences induced by NMDA receptor antagonist in healthy volunteers. Biological Psychiatry 2002; 51(5):400-406
190. Umbricht D, Vollenweider FX, Schmid L, Grubel C, Skrabo A, Huber T, Koller R: Effects of the 5-HT2A agonist psilocybin on mismatch negativity generation and AX-continuous performance task: Implications for the neuropharmacology of cognitive deficits in schizophrenia. Neuropsychopharmacology 2003; 28(1):170-181
191. Halpern JH, Pope HG: Hallucinogen persisting perception disorder: what do we know after 50 years? Drug and Alcohol Dependence 2003; 69(2):109-119
192. AbiDargham A, Laruelle M, Charney D, Krystal J: Serotonin and schizophrenia: A review. Drugs of Today 1996; 32(2):171-185
193. Iqbal N, vanPraag HM: The role of serotonin in schizophrenia. European Neuropsychopharmacology 1995; 5:11-23
194. Amargos-Bosch M, Lopez-Gil X, Artigas F, Adell A: Clozapine and olanzapine, but not haloperidol, suppress serotonin efflux in the medial prefrontal cortex elicited by phencyclidine and ketamine. International Journal of Neuropsychopharmacology 2006; 9(5):565-573
195. Lopez-Gil X, Babot Z, Amargos-Bosch M, Sunol C, Artigas F, Adell A: Clozapine and haloperidol differently suppress the MK-801 increased glutamatergic and serotonergic transmission in the medial prefrontal cortex of the rat. Neuropsychopharmacology 2007; 32(10):2087-2097
196. Breese GR, Knapp DJ, Moy SS: Integrative role for serotonergic and glutamatergic receptor mechanisms in the action of NMDA antagonists: potential relationships to antipsychotic drug actions on NMDA antagonist responsiveness. Neuroscience and Biobehavioral Reviews 2002; 26(4):441-455

197. Noda Y, Kamei H, Mamiya T, Furukawa H, Nabeshima T: Repeated phencyclidine treatment induces negative symptom-like behavior in forced swimming test in mice: Imbalance of prefrontal serotonergic and dopaminergic functions. Neuropsychopharmacology 2000; 23(4):375-387
198. Martin P, Carlsson ML, Hjorth S: Systemic PCP treatment elevates brain extracellular 5-HT: a microdialysis study in awake rats. Neuroreport 1998; 9(13):2985-2988
199. Nichols CD, Sanders-Bush E: A single dose of lysergic acid diethylamide influences gene expression patterns within the mammalian brain. Neuropsychopharmacology 2002; 26(5):634-642
200. Gonzalez-Maeso J, Ang RL, Yuen T, Chan P, Weisstaub NV, Lopez-Gimenez JF, Zhou M, Okawa Y, Calldo LF, Milligan G, Gingrich JA, Filizola M, Meana JJ, Sealfon SC: Identification of a serotonin/glutamate receptor complex implicated in psychosis. Nature 2008:doi:10.1038/nature06612
201. Solowij N: Ecstasy (3,4-methylenedioxymethamphetamine). Current Opinion in Psychiatry 1993; 6:411-415
202. Gamma A, Buck A, Berthold T, Hell D, Vollenweider FX: 3,4-methylenedioxymethamphetamine (MDMA) modulates cortical and limbic brain activity as measured by [(H2O)-O-15]-PET in healthy humans. Neuropsychopharmacology 2000; 23(4):388-395
203. Parrott AC: Human psychopharmacology of Ecstasy (MDMA): a review of 15 years of empirical research. Human Psychopharmacology-Clinical and Experimental 2001; 16(8):557-577
204. Bialer PA: Designer drugs in the general hospital. Psychiatric Clinics of North America 2002; 25(1):231-243
205. Thomasius R, Petersen KU, Zapletalova P, Wartberg L, Zeichner D, Schmoldt A: Mental disorders in current and former heavy ecstasy (MDMA) users. Addiction 2005; 100(9):1310-1319
206. Cottler LB, Womack SB, Compton WM, Ben-Abdallah A: Ecstasy abuse and dependence among adolescents and young adults: applicability and reliability of DSM-IV criteria. Human Psychopharmacology-Clinical and Experimental 2001; 16(8):599-606
207. World Health Organization: Amphetamine like stimulants. Report from the WHO meeting on amphetamines, MDMA and other psychostimulants. Geneva, WHO, 1996
208. Cole JC, Sumnall HR: Altered states: the clinical effects of ecstasy. Pharmacology & Therapeutics 2003; 98(1):35-58
209. Green AR, Mechan AO, Elliott JM, O'Shea E, Colado MI: The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). Pharmacological Reviews 2003; 55(3):463-508
210. Landry MJ: MDMA: A review of epidemiologic data. Journal of Psychoactive Drugs 2002; 34(2):163-169
211. Australian Institute of Health and Welfare: 2004 National Drug Strategy Household Survey: Detailed Findings. AIHW cat. no. PHE 66. Canberra, AIHW, 2005

212. Australian Institute of Health and Welfare: 2001 National Drug Strategy Household Survey; First results. AIHW cat. no. PHE 35. Canberra, AIHW, 2002
213. Wish ED, Fitzelle DB, O'Grady KE, Hsu MH, Arria AM: Evidence for significant polydrug use among ecstasy-using college students. Journal of American College Health 2006; 55(2):99-104
214. Topp L, Hando J, Dillon P, Roche A, Solowij N: Ecstasy use in Australia: patterns of use and associated harm. Drug and Alcohol Dependence 1999; 55(1-2):105-115
215. Solowij N, Hall W, Lee N: Recreational MDMA use in Sydney - A profile of ecstasy users and their experiences with the drug. British Journal of Addiction 1992; 87(8):1161-1172
216. Schifano F: A bitter pill. Overview of ecstasy (MDMA, MDA) related fatalities. Psychopharmacology 2004; 173(3-4):242-248
217. Henry JA, Jeffreys KJ, Dawling S: Toxicity and deaths from 3,4-methylenedioxymethamphetamine (ecstasy). Lancet 1992; 340(8816):384-387
218. Schifano F, Oyefeso A, Corkery J, Cobain K, Jambert-Gray R, Martinotti G, Ghodse AH: Death rates from ecstasy (MDMA, MDA) and polydrug use in England and Wales 1996-2002. Human Psychopharmacology-Clinical and Experimental 2003; 18(7):519-524
219. Schifano F, Corkery J, Deluca P, Oyefeso A, Ghodse AH: Ecstasy (MDMA, MDA, MDEA, MBDB) consumption, seizures, retated offences, prices, dosage levels and deaths in the UK (1994-2003). Journal of Psychopharmacology 2006; 20(3):456-463
220. Morgan MJ: Ecstasy (MDMA): a review of its possible persistent psychological effects. Psychopharmacology 2000; 152(3):230-248
221. Medina KL, Shear PK: Anxiety, depression, and behavioral symptoms of executive dysfunction in ecstasy users: Contributions of polydrug use. Drug and Alcohol Dependence 2007; 87(2-3):303-311
222. Roiser JP, Rogers RD, Sahakian BJ: Neuropsychological function in ecstasy users: a study controlling for polydrug use. Psychopharmacology 2007; 189(4):505-516
223. Kalechstein AD, De La Garza R, Mahoney JJ, Fantegrossi WE, Newton TF: MDMA use and neurocognition: a meta-analytic review. Psychopharmacology 2007; 189(4):531-537
224. Thomasius R, Petersen K, Buchert R, Andresen B, Zapletalova P, Wartberg L, Nebeling B, Schmoldt A: Mood, cognition and serotonin transporter availability in current and former ecstasy (MDMA) users. Psychopharmacology 2003; 167(1):85-96
225. Parrott AC, Buchanan T, Scholey AB, Heffernan T, Ling J, Rodgers J: Ecstasy/MDMA attributed problems reported by novice, moderate and heavy recreational users. Human Psychopharmacology - Clinical and Experimental 2002; 17(6):309-312
226. Quednow BB, Jessen F, Kuhn KU, Maier W, Daum I, Wagner M: Memory deficits in abstinent MDMA (ecstasy) users: neuropsychological evidence of frontal dysfunction. Journal of Psychopharmacology 2006; 20(3):373-384

227. Zakzanis KK, Young DA: Memory impairment in abstinent MDMA ("ecstasy") users: A longitudinal investigation. Neurology 2001; 56(7):966-969
228. Fox HC, McLean A, Turner JJD, Parrott AC, Rogers R, Sahakian BJ: Neuropsychological evidence of a relatively selective profile of temporal dysfunction in drug-free MDMA ("ecstasy") polydrug users. Psychopharmacology 2002; 162(2):203-214
229. Schuler S: Early recognition and early intervention in drug-induced psychoses. Neurology Psychiatry and Brain Research 1998; 5(4):197-204
230. Yucel M, L:ubman DI, Solowij N, Brewer WJ: Understanding drug addiction: a neuropsychological perspective. Australian and New Zealand Journal of Psychiatry 2007; 41:957-968
231. Lieb R, Schuetz CG, Pfister H, von Sydow K, Wittchen HU: Mental disorders in ecstasy users: a prospective-longitudinal investigation. Drug and Alcohol Dependence 2002; 68(2):195-207
232. Falck RS, Carlson RG, Wang JC, Siegal HA: Psychiatric disorders and their correlates among young adult MDMA users in Ohio. Journal of Psychoactive Drugs 2006; 38(1):19-29
233. Sumnell HR, Cole JC: Self-reported depressive symptomatology in community samples of polysubstance misusers who report ecstasy use: a meta-analysis. Journal of Psychopharmacology 2005; 19(1):84-92
234. Soar K, Turner JJD, Parrott AC: Psychiatric disorders in ecstasy (MDMA) users: a literature review focusing on personal predisposition and drug history. Human Psychopharmacology - Clinical and Experimental 2001; 16(8):641-645
235. Landabaso MA, Iraurgi I, Jimenez-Lerma JM, Calle R, Sanz J, Gutierrez-Fraile M: Ecstasy-induced psychotic disorder: Six-month follow-up study. European Addiction Research 2002; 8(3):133-140
236. Gouzoulis E, Borchardt D, Hermle L: A case of toxic psychosis induced by Eve (3,4-Methylene-Dioxyethylam-Phetamine). Archives of General Psychiatry 1993; 50(1):75-75
237. Liechti ME, Geyer MA, Hell D, Vollenweider FX: Effects of MDMA (ecstasy) on prepulse inhibition and habituation of startle in humans after pretreatment with citalopram, haloperidol, or ketanserin. Neuropsychopharmacology 2001; 24(3):240-252
238. Vollenweider FX, Remensberger S, Hell D, Geyer MA: Opposite effects of 3,4-methylenedioxymethamphetamine (MDMA) on sensorimotor gating in rats versus healthy humans. Psychopharmacology 1999; 143(4):365-372
239. Quednow BB, Kuhn KU, Hoenig K, Maier W, Wagner M: Prepulse inhibition and habituation of acoustic startle response in male MDMA ('ecstasy') users, cannabis users, and healthy controls. Neuropsychopharmacology 2004; 29(5):982-990
240. van den Buuse M, Garner B, Gogos A, Kusljic S: Importance of animal models in schizophrenia research. Australian and New Zealand Journal of Psychiatry 2005; 39(7):550-557
241. Boutros NN, Galloway M, Pihlgren EM: Stimulants and Psychosis, in Secondary Schizophrenia. Edited by Sachdev PS, Keshavan MS. Cambridge, Cambridge University Press, in press

242. O'Neill MF, Shaw G: Comparison of dopamine receptor antagonists on hyperlocomotion induced by cocaine, amphetamine, MK-801 and the dopamine D-1 agonist C-APB in mice. Psychopharmacology 1999; 145(3):237-250
243. Russell RW: Extrapolation from animals to man, in Animal behavior and drug action. Edited by Steinberg H. Boston, Little, Brown, 1964, pp 410-418
244. Creese I, Iversen SD: Pharmacological and anatomical substrates of amphetamine response in rat. Brain Research 1975; 83(3):419-436
245. Kohler C, Fuxe K, Ross SB: Regional in vivo binding of [3H]N-Propylnorapomorphine in the mouse brain - Evidence for labeling of central dopamine receptors. European Journal of Pharmacology 1981; 72(4):397-402
246. Van der werf JF, Sebens JB, Vaalburg W, Korf J: In vivo binding of N-N-Propylnorapomorphine in the rat brain - Regional localization, quantification in striatum and lack of correlation with dopamine metabolism. European Journal of Pharmacology 1983; 87(2-3):259-270
247. Logan J, Dewey SL, Wolf AP, Fowler JS, Brodie JD, Angrist B, Volkow ND, Gatley SJ: Effects of endogenous dopamine on measures of [F-18] N-Methylspiroperidol binding in the basal ganglia - Comparison of simulations and experimental results from PET studies in baboons. Synapse 1991; 9(3):195-207
248. Dewey SL, Smith GS, Logan J, Brodie JD, Fowler JS, Wolf AP: Striatal binding of the PET ligand C-11 raclopride is altered by drugs that modify synaptic dopamine levels. Synapse 1993; 13(4):350-356
249. Innis RB, Malison RT, Altikriti M, Hoffer PB, Sybirska EH, Seibyl JP, Zoghbi SS, Baldwin RM, Laruelle M, Smith EO, Charney DS, Heninger G, Elsworth JD, Roth RH: Amphetamine stimulated dopamine release competes in vivo for [I-123] IBZM binding to the D2-receptor in nonhuman primates. Synapse 1992; 10(3):177-184
250. Laruelle M, AbiDargham A, vanDyck CH, Gil R, Dsouza CD, Erdos J, McCance E, Rosenblatt W, Fingado C, Zoghbi SS, Baldwin RM, Seibyl JP, Krystal JH, Charney DS, Innis RB: Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects. Proceedings of the National Academy of Sciences of the United States of America 1996; 93(17):9235-9240
251. Javitt DC, Laruelle M: Neurochemical theories, in Textbook of Schizophrenia. Edited by Lieberman JA, Stroup ST, Perkins DO. Washington DC, American Psychiatric Publishing, 2006, pp 85-116
252. Abi-Dargham A, Gil R, Krystal J, Baldwin RM, Seibyl JP, Bowers M, van Dyck CH, Charney DS, Innis RB, Laruelle M: Increased striatal dopamine transmission in schizophrenia: Confirmation in a second cohort. American Journal of Psychiatry 1998; 155(6):761-767
253. Homayoun H, Moghaddam B: Progression of cellular adaptations in medial prefrontal and orbitofrontal cortex in response to repeated amphetamine. Journal of Neuroscience 2006; 26(31):8025-8039
254. Hill K, Mann L, Laws KR, Stephenson ME, Nimmo-Smith I, McKenna PJ: Hypofrontality in schizophrenia: a meta-analysis of functional imaging studies. Acta Psychiatrica Scandinavica 2004; 110:243-256

255. Dom G, Sabbe B, Hulstijn W, van den Brink W: Substance use disorders and the orbitofrontal cortex. British Journal of Psychiatry 2005; 187:209-220
256. McLellan AT, Woody GE, Obrien CP: Development of psychiatric illness in drug abusers - Possible role of drug preference. New England Journal of Medicine 1979; 301(24):1310-1314
257. Angrist B, Sathananthan G, Wilk S, Gershon S: Amphetamine psychosis - Behavioral and biochemical aspects. Journal of Psychiatric Research 1974; 11:13-23
258. Bell DS: Experimental reproduction of amphetamine psychosis. Archives of General Psychiatry 1973; 29(1):35-40
259. Griffith JD, Oates JA, Cavanaug.J, Held J: Dextroamphetamine - Evaluation of psychomimetic properties in man. Archives of General Psychiatry 1972; 26(2):97-100
260. Ellinwood EH: Amphetamine psychosis. I. Description of individuals and process. Journal of Nervous and Mental Disease 1967; 144(4):273-283
261. Angrist BM, Gershon S: The phenomenology of experimentally induced amphetamine psychosis - preliminary observations. Biological Psychiatry 1970; 2:95-107
262. Steketee JD: Neurotransmitter systems of the medial prefrontal cortex: potential role in sensitization to psychostimulants. Brain Research Reviews 2003; 41(2-3):203-228
263. Wolf ME: The role of excitatory amino acids in behavioral sensitization to psychomotor stimulants. Progress in Neurobiology 1998; 54(6):679-720
264. Kalivas PW: Interactions between dopamine and excitatory amino acids in behavioral sensitization to psychostimulants. Drug and Alcohol Dependence 1995; 37(2):95-100
265. Jentsch JD, Roth RH: The neuropsychopharmacology of phencyclidine: From NMDA receptor hypofunction to the dopamine hypothesis of schizophrenia. Neuropsychopharmacology 1999; 20(3):201-225
266. Jackson ME, Homayoun H, Moghaddam B: NMDA receptor hypofunction produces concomitant firing rate potentiation and burst activity reduction in the prefrontal cortex. Proceedings of the National Academy of Sciences of the United States of America 2004; 101(22):8467-8472
267. MacDonald AW, Chafee MV: Translational and developmental perspective on N-methyl-D-aspartate synaptic deficits in schizophrenia. Development and Psychopathology 2006; 18(3):853-876
268. Kapur S, Seeman P: Ketamine has equal affinity for NMDA receptors and the high-affinity state of the dopamine D-2 receptor. Biological Psychiatry 2001; 49(11):954-955
269. Kapur S, Seeman P: NMDA receptor antagonists ketamine and PCP have direct effects on the dopamine D-2 and serotonin 5-HT2 receptors - implications for models of schizophrenia. Molecular Psychiatry 2002; 7(8):837-844
270. Seeman P, Ko F, Tallerico T: Dopamine receptor contribution to the action of PCP, LSD and ketamine psychotomimetics. Molecular Psychiatry 2005; 10(9):877-883

271. Seeman P, Lasaga M: Dopamine agonist action of phencyclidine. Synapse 2005; 58(4):275-277
272. Seeman P, Weinshenker D, Quirion R, Srivastava IAK, Bhardwaj SK, Grandy DK, Premont RT, Sotnikova TD, Boksa P, El-Ghundi M, O'Dowd BF, George SR, Perreault ML, Mannisto PT, Robinson S, Palmiter RD, Tallerico T: Dopamine supersensitivity correlates with D2(High) states, implying many paths to psychosis. Proceedings of the National Academy of Sciences of the United States of America 2005; 102(9):3513-3518
273. Seeman P: Comment on "diverse psychotomimetics act through a common signaling pathway". Science 2004; 305(5681)
274. Seeman P, Schwarz J, Chen JF, Szechtman H, Perreault M, McKnight GS, Roder JC: Psychosis pathways converge via D2(High) dopamine receptors. Synapse 2006; 60(4):319-346
275. Svenningsson P, Nomikos GG, Greengard P: Response to comment on "Diverse psychotomimetics act through a common signaling pathway". Science 2004; 305(5681)
276. Jordan S, Chen R, Fernalld R, Johnson J, Regardie K, Kambayashi J, Tadori Y, Kitagawa H, Kikuchi T: In vitro biochemical evidence that the psychotomimetics phencyclidine, ketamine and dizocilpine (MK-801) are inactive at cloned human and rat dopamine D-2 receptors. European Journal of Pharmacology 2006; 540(1-3):53-56
277. Svenningsson P, Nishi A, Fisone G, Girault JA, Nairn AC, Greengard P: DARPP-32: An integrator of neurotransmission. Annual Review of Pharmacology and Toxicology 2004; 44:269-296
278. Svenningsson P, Tzavara ET, Carruthers R, Rachleff I, Wattler S, Nehls M, McKinzie DL, Fienberg AA, Nomikos GG, Greengard P: Diverse psychotomimetics act through a common signaling pathway. Science 2003; 302(5649):1412-1415
279. Rabiner EA: Imaging of striatal dopamine release elicited with NMDA antagonists: there anything there to be seen? Journal of Psychopharmacology 2007; 21(3):253-258
280. Davis SM, Lees KR, Albers GW, Diener HC, Markabi S, Karlsson G, Norris J: Selfotel in acute ischemic stroke - Possible neurotoxic effects of an NMDA antagonist. Stroke 2000; 31(2):347-354
281. Moghaddam B, Adams BW: Reversal of phencyclidine effects by a group II metabotropic glutamate receptor agonist in rats. Science 1998; 281(5381):1349-1352
282. Sams-Dodd F: Distinct Effects of D-amphetamine and phencyclidine on the social behavior of rats. Behavioural Pharmacology 1995; 6(1):55-65
283. Sams-Dodd F: Phencyclidine-induced stereotyped behaviour and social isolation in rats: A possible animal model of schizophrenia. Behavioural Pharmacology 1996; 7(1):3-23
284. Sams-Dodd F: Effects of continuous D-amphetamine and phencyclidine administration on social behaviour, stereotyped behaviour, and locomotor activity in rats. Neuropsychopharmacology 1998; 19(1):18-25

285. Sams-Dodd F: Effects of dopamine agonists and antagonists on PCP-induced stereotyped behaviour and social isolation in the rat social interaction test. Psychopharmacology 1998; 135(2):182-193
286. Ealster RL, Chait LD: The behavioral effects of phencyclidine in animals, in Phencyclidine (PCP) Abuse: An Appraisal, Monograph 21. Edited by Petersen RC, Stillman RC. Rockville, Maryland, National Institute on Drug Abuse, 1978, pp 53-65
287. Hetzler BE, Wautlet BS: Ketamine-induced locomotion in rats in an open field. Pharmacology Biochemistry and Behavior 1985; 22(4):653-655
288. Rung JP, Carlsson A, Markinhuhta KR, Carlsson ML: (+)-MK-801 induced social withdrawal in rats; a model for negative symptoms of schizophrenia. Progress in Neuro-Psychopharmacology & Biological Psychiatry 2005; 29(5):827-832
289. Duncan GE, Miyamoto S, Lieberman JA: Chronic administration of haloperidol and olanzapine attenuates ketamine-induced brain metabolic activation. Journal of Pharmacology and Experimental Therapeutics 2003; 305(3):999-1005
290. Sams-Dodd F: Phencyclidine in the social interaction test: An animal model of schizophrenia with face and predictive validity. Reviews in the Neurosciences 1999; 10(1):59-90
291. Stefani MR, Moghaddam B: Effects of repeated treatment with amphetamine or phencyclidine on working memory in the rat. Behavioural Brain Research 2002; 134(1-2):267-274
292. Egerton A, Reid L, McKerchar CE, Morris BJ, Pratt JA: Impairment in perceptual attentional set-shifting following PCP administration: a rodent model of set-shifting deficits in schizophrenia. Psychopharmacology 2005; 179(1):77-84
293. Jentsch JD, Tran A, Le D, Youngren KD, Roth RH: Subchronic phencyclidine administration reduces mesoprefrontal dopamine utilization and impairs prefrontal cortical-dependent cognition in the rat. Neuropsychopharmacology 1997; 17(2):92-99
294. Jentsch JD, Redmond DE, Elsworth JD, Taylor JR, Youngren KD, Roth RH: Enduring cognitive deficits and cortical dopamine dysfunction in monkeys after long-term administration of phencyclidine. Science 1997; 277(5328):953-955
295. Stefani MR, Groth K, Moghaddam B: Glutamate receptors in the rat medial prefrontal cortex regulate set-shifting ability. Behavioral Neuroscience 2003; 117(4):728-737
296. Rujescu D, Bender A, Keck M, Hartmann AM, Ohl F, Raeder H, Giegling I, Genius J, McCarley RW, Moller HJ, Grunze H: A pharmacological model for psychosis based on N-methyl-D-aspartate receptor hypofunction: Molecular, cellular, functional and Behavioral abnormalities. Biological Psychiatry 2006; 59(8):721-729
297. Geyer MA, Swerdlow NR, Mansbach RS, Braff DL: Startle response models of sensorimotor gating and habituation deficits in schizophrenia. Brain Research Bulletin 1990; 25(3):485-498
298. Mansbach RS, Geyer MA: Effects of phencyclidine and phencyclidine analogues on sensorimotor gating in the rat. Neuropsychopharmacology 1989; 2(4):299-308

299. Geyer MA, Braff DL, Mansbach RS: Failure of haloperidol to block the disruption of sensory gating induced by phencyclidine and MK-801. Biological Psychiatry 1989; 25:169A
300. Cilia J, Hatcher P, Reavill C, Jones DNC: (+/-) ketamine-induced prepulse inhibition deficits of an acoustic startle response in rats are not reversed by antipsychotics. Journal of Psychopharmacology 2007; 21(3):302-311
301. Brody SA, Geyer MA, Large CH: Lamotrigine prevents ketamine but not amphetamine-induced deficits in prepulse inhibition in mice. Psychopharmacology 2003; 169(3-4):240-246
302. Mansbach RS, Geyer MA, Braff DL: Dopaminergic stimulation disrupts sensorimotor gating in the rat. Psychopharmacology 1988; 94(4):507-514
303. Geyer MA, Braff DL: Startle habituation and sensorimotor gating in schizophrenia and related animal models. Schizophrenia Bulletin 1987; 13(4):643-668
304. Duncan GE, Miyamoto S, Leipzig JN, Lieberman JA: Comparison of brain metabolic activity patterns induced by ketamine, MK-801 and amphetamine in rats: support for NMDA receptor involvement in responses to subanesthetic dose of ketamine. Brain Research 1999; 843(1-2):171-183
305. Duncan GE, Leipzig JN, Mailman RB, Lieberman JA: Differential effects of clozapine and haloperidol on ketamine-induced brain metabolic activation. Brain Research 1998; 812(1-2):65-75
306. Duncan GE, Moy SS, Knapp DJ, Mueller RA, Breese GR: Metabolic mapping of the rat brain after subanesthetic doses of ketamine: potential relevance to schizophrenia. Brain Research 1998; 787(2):181-190
307. Littlewood CL, Jones N, O'Neill MJ, Mitchell SN, Tricklebank M, Williams SCR: Mapping the central effects of ketamine in the rat using pharmacological MRI. Psychopharmacology 2006; 186(1):64-81
308. Burdett NG, Menon DK, Carpenter TA, Jones JG, Hall LD: Visualization of changes in regional cerebral blood flow (rCBF) produced by ketamine using long TE gradient echo sequences – Preliminary results. Magnetic Resonance Imaging 1995; 13(4):549-553
309. Lewis DA, Gonzalez-Burgos G: Pathophysiologically based treatment interventions in schizophrenia. Nature Medicine 2006; 12(9):1016-1022
310. Lewis DA, Hashimoto T: Deciphering the disease process of schizophrenia: The contribution of cortical GABA neurons. Integrating the Neurobiology of Schizophrenia 2007; 78:109-+
311. Lewis DA, Hashimoto T, Volk DW: Cortical inhibitory neurons and schizophrenia. Nature Reviews Neuroscience 2005; 6(4):312-324
312. Lewis DA, Gonzalez-Burgos G: Neuroplasticity of neocortical circuits in schizophrenia. Neuropsychopharmacology 2008; 33:141-165
313. Harrison PJ: The hippocampus in schizophrenia: a review of the neuropathological evidence and its pathophysiological implications. Psychopharmacology 2004; 174(1):151-162
314. Weinberger DR: Cell biology of the hippocampal formation in schizophrenia. Biological Psychiatry 1999; 45(4):395-402

315. Shenton ME, Dickey CC, Frumin M, McCarley RW: A review of MRI findings in schizophrenia. Schizophrenia Research 2001; 49(1-2):1-52
316. Bogerts B: Recent Advances in the neuropathology of schizophrenia. Schizophrenia Bulletin 1993; 19(2):431-445
317. Buchsbaum MS, Someya T, Teng CY, Abel L, Chin S, Najafi A, Haier RJ, Wu J, Bunney WE: PET and MRI of the thalamus in never-medicated patients with schizophrenia. American Journal of Psychiatry 1996; 153(2):191-199
318. Wu JC, Buchsbaum MS, Potkin SG, Wolf MJ, Bunney WE: Positron emission tomography study of phencyclidine users. Schizophrenia Research 1991; 4(3):415-415
319. Hertzman M, Reba RC, Kotlyarov EV: Single photon emission computed tomography in phencyclidine and related drug abuse. American Journal of Psychiatry 1990; 147(2):255-256
320. Cochran SM, Kennedy M, McKerchar CE, Steward LJ, Pratt JA, Morris BJ: Induction of metabolic hypofunction and neurochemical deficits after chronic intermittent exposure to phencyclidine: Differential modulation by antipsychotic drugs. Neuropsychopharmacology 2003; 28(2):265-275
321. Wickelgren I: Neurobiology - A new route to treating schizophrenia? Science 1998; 281(5381):1264-1265
322. Moghaddam B, Adams B, Verma A, Daly D: 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. Journal of Neuroscience 1997; 17(8):2921-2927
323. Adams B, Moghaddam B: Corticolimbic dopamine neurotransmission is temporally dissociated from the cognitive and locomotor effects of phencyclidine. Journal of Neuroscience 1998; 18(14):5545-5554
324. Liu J, Moghaddam B: Regulation of glutamate efflux by excitatory amino acid receptors - Evidence for tonic inhibitory and phasic excitatory regulation. Journal of Pharmacology and Experimental Therapeutics 1995; 274(3):1209-1215
325. Homayoun L, Jackson ME, Moghaddam B: Activation of metabotropic glutamate 2/3 receptors reverses the effects of NMDA receptor hypofunction on prefrontal cortex unit activity in awake rats. Journal of Neurophysiology 2005; 93(4):1989-2001
326. Homayoun H, Moghaddam B: Fine-tuning of awake prefrontal cortex neurons by clozapine: Comparison with haloperidol and N-desmethylclozapine. Biological Psychiatry 2007; 61(5):679-687
327. Homayoun H, Moghaddam B: NMDA receptor hypofunction produces opposite effects on prefrontal cortex Interneurons and pyramidal neurons. Journal of Neuroscience 2007; 27(43):11496-11500
328. Suzuki Y, Jodo E, Takeuchi S, Niwa S, Kayama Y: Acute administration of phencyclidine induces tonic activation of medial prefrontal cortex neurons in freely moving rats. Neuroscience 2002; 114(3):769-779
329. Jodo E, Suzuki Y, Katayama T, Hoshino KY, Takeuchi S, Niwa SI, Kayama Y: Activation of medial prefrontal cortex by phencyclidine is mediated via a hippocampo-prefrontal pathway. Cerebral Cortex 2005; 15(5):663-669

330. Katayama T, Jodo E, Suzuki Y, Hoshino KY, Takeuchi S, Kayama Y: Activation of medial prefrontal cortex neurons by phencyclidine is mediated via AMPA/kainate glutamate receptors in anesthetized rats. Neuroscience 2007; 150(2):442-448
331. Olney JW, Newcomer JW, Farber NB: NMDA receptor hypofunction model of schizophrenia. Journal of Psychiatric Research 1999; 33(6):523-533
332. Halberstadt AL: The phencyclidine glutamate model of schizophrenia. Clinical Neuropharmacology 1995; 18(3):237-249
333. Tsai GC, Coyle JT: Glutamatergic mechanisms in schizophrenia. Annual Review of Pharmacology and Toxicology 2002; 42:165-179
334. Hirsch SR, Das I, Garey LJ, deBelleroche J: A pivotal role for glutamate in the pathogenesis of schizophrenia, and its cognitive dysfunction. Pharmacology Biochemistry and Behavior 1997; 56(4):797-802
335. Vollenweider FX, Geyer MA: A systems model of altered consciousness: Integrating natural and drug-induced psychoses. Brain Research Bulletin 2001; 56(5):495-507
336. Stone JM, Morrison PD, Pilowsky LS: Glutamate and dopamine dysregulation in schizophrenia - A synthesis and selective review. Journal of Psychopharmacology 2007; 21(4):440-452
337. Morris BJ, Cochran SM, Pratt JA: PCP: from pharmacology to modelling schizophrenia. Current Opinion in Pharmacology 2005; 5(1):101-106
338. Large CH: Do NMDA receptor antagonist models of schizophrenia predict the clinical efficacy of antipsychotic drugs? Journal of Psychopharmacology 2007; 21(3):283-301
339. Gulyas AI, Megias M, Emri Z, Freund TF: Total number and ratio of excitatory and inhibitory synapses converging onto single interneurons of different types in the CA1 area of the rat hippocampus. Journal of Neuroscience 1999; 19(22):10082-10097
340. Jones RSG, Buhl EH: Basket-like interneurons in layer II of the entorhinal cortex exhibit a powerful NMDA-mediated synaptic excitation. Neuroscience Letters 1993; 149(1):35-39
341. Goldberg JH, Yuste R, Tamas G: Ca^{2+} imaging of mouse neocortical interneurone dendrites: Contribution of Ca^{2+}-permeable AMPA and NMDA receptors to subthreshold Ca^{2+} dynamics. Journal of Physiology-London 2003; 551(1):67-78
342. Cochran SM, Fujimura M, Morris BJ, Pratt JA: Acute and delayed effects of phencyclidine upon mRNA levels of markers of glutamatergic and GABAergic neurotransmitter function in the rat brain. Synapse 2002; 46(3):206-214
343. Abdul-Monim Z, Neill JC, Reynolds GP: Sub-chronic psychotomimetic phencyclidine induces deficits in reversal learning and alterations in parvalbumin-immunoreactive expression in the rat. Journal of Psychopharmacology 2007; 21(2):198-205
344. Keilhoff G, Becker A, Grecksch G, Wolf G, Bernstein HG: Repeated application of ketamine to rats induces changes in the hippocampal expression of parvalbumin, neuronal nitric oxide synthase and cFOS similar to those found in human Schizophrenia. Neuroscience 2004; 126(3):591-598

345. Morrow BA, Elsworth JD, Roth RH: Repeated phencyclidine in monkeys results in loss of parvalbumin-containing axo-axonic projections in the prefrontal cortex. Psychopharmacology 2007; 192(2):283-290
346. Behrens MM, Ali SS, Dao DN, Lucero J, Shekhtman G, Quick KL, Dugan LL: Ketamine-induced loss of phenotype of fast-spiking interneurons is mediated by NADPH-oxidase. Science 2007; 318(5856):1645-1647
347. Kinney JW, Davis CN, Tabarean I, Conti B, Bartfai T, Behrens MM: A specific role for NR2A-containing NMDA receptors in the maintenance of parvalbumin and GAD67 immunoreactivity in cultured interneurons. Journal of Neuroscience 2006; 26(5):1604-1615
348. Bartos M, Vida I, Jonas P: Synaptic mechanisms of synchronized gamma oscillations in inhibitory interneuron networks. Nature Reviews Neuroscience 2007; 8(1):45-56
349. Cunningham MO, Hunt J, Middleton S, LeBeau FEN, Gillies MG, Davies CH, Maycox PR, Whittington MA, Racca C: Region-specific reduction in entorhinal gamma oscillations and parvalbumin-immunoreactive neurons in animal models of psychiatric illness. Journal of Neuroscience 2006; 26(10):2767-2776
350. Reynolds GP, Harte MK: The neuronal pathology of schizophrenia: molecules and mechanisms. Biochemical Society Transactions 2007; 35:433-436
351. Basar-Eroglu C, Brand A, Hildebrandt H, Kedzior KK, Mathes B, Schmiedt C: Working memory related gamma oscillations in schizophrenia patients. International Journal of Psychophysiology 2007; 64(1):39-45
352. Symond MB, Harris AWF, Gordon E, Williams LM: "Gamma synchrony" in first-episode schizophrenia: A disorder of temporal connectivity? American Journal of Psychiatry 2005; 162(3):459-465
353. Light GA, Hsu JL, Hsieh MH, Meyer-Gomes K, Sprock J, Swerdlow NR, Braff DL: Gamma band oscillations reveal neural network cortical coherence dysfunction in schizophrenia patients. Biological Psychiatry 2006; 60(11):1231-1240
354. Spencer KM: Abnormal neural synchrony in schizophrenia. Psychophysiology 2003; 40:S17-S17
355. Jentsch JD, Elsworth JD, Redmond DE, Roth RH: Phencyclidine increases forebrain monoamine metabolism in rats and monkeys: Modulation by the isomers of HA966. Journal of Neuroscience 1997; 17(5):1769-1775
356. Kusljic S, Copolov DL, van den Buuse M: Differential role of serotonergic projections arising from the dorsal and median raphe nuclei in locomotor hyperactivity and prepulse inhibition. Neuropsychopharmacology 2003; 28(12):2138-2147
357. Rabin RA, Doat M, Winter JC: Role of serotonergic 5-HT2A receptors in the psychotomimetic actions of phencyclidine. International Journal of Neuropsychopharmacology 2000; 3(4):333-338
358. Farber NB, Hanslick J, Kirby C, McWilliams L, Olney JW: Serotonergic agents that activate 5HT(2A) receptors prevent NMDA antagonist neurotoxicity. Neuropsychopharmacology 1998; 18(1):57-62
359. Kristiansen LV, Huerta I, Beneyto M, Meador-Woodruff JH: NMDA receptors and schizophrenia. Current Opinion in Pharmacology 2007; 7(1):48-55

360. Javitt DC: Glutamate and schizophrenia: Phencyclidine, N-methyl-D-aspartate receptors, and dopamine-glutamate interactions, in Integrating the Neurobiology of Schizophrenia, vol 78, 2007, pp 69-+
361. Catts SV, Ward PB, Lloyd A, Huang XF, Dixon G, Chahl L, Harper C, Wakefield D: Molecular biological investigations into the role of the NMDA receptor in the pathophysiology of schizophrenia. Australian and New Zealand Journal of Psychiatry 1997; 31(1):17-26
362. Carlsson A: The current status of the dopamine hypothesis of schizophrenia. Neuropsychopharmacology 1988; 1(3):179-186
363. Carlsson M, Carlsson A: Schizophrenia – A subcortical neurotransmitter imbalance syndrome. Schizophrenia Bulletin 1990; 16(3):425-432
364. Anand A, Charney DS, Oren DA, Berman RM, Hu XS, Cappiello A, Krystal JH: Attenuation of the neuropsychiatric effects of ketamine with lamotrigine - Support for hyperglutamatergic effects of N-methyl-D-aspartate receptor antagonists. Archives of General Psychiatry 2000; 57(3):270-276
365. Large CH, Webster EL, Goff DC: The potential role of lamotrigine in schizophrenia. Psychopharmacology 2005; 181(3):415-436
366. Kremer I, Vass A, Gorelik I, Bar G, Blanaru M, Javitt DC, Heresco-Levy U: Placebo-controlled trial of lamotrigine added to conventional and atypical antipsychotics in schizophrenia. Biological Psychiatry 2004; 56(6):441-446
367. Dursun SM, Deakin JFW: Augmenting antipsychotic treatment with lamotrigine or topiramate in patients with treatment-resistant schizophrenia: a naturalistic caseseries outcome study. Journal of Psychopharmacology 2001; 15(4):297-301
368. Dursun SM, McIntosh D: Clozapine plus lamotrigine in treatment-resistant schizophrenia. Archives of General Psychiatry 1999; 56(10):950-950
369. Zoccali R, Muscatello MR, Bruno A, Cambria R, Mico U, Spina E, Meduri M: The effect of lamotrigine augmentation of clozapine in a sample of treatment-resistant schizophrenic patients: A double-blind, placebo-controlled study. Schizophrenia Research 2007; 93(1-3):109-116
370. Tiihonen J, Hallikainen T, Ryynanen OP, Repo-Tiihonen E, Kotilainen I, Eronen M, Toivonen P, Wahlbeck K, Putkonen A: Lamotrigine in treatment-resistant schizophrenia: A randomized placebo-controlled crossover trial. Biological Psychiatry 2003; 54(11):1241-1248
371. Ahmad S, Fowler LJ, Whitton PS: Lamotrigine, carbamazepine and phenytoin differentially alter extracellular levels of 5-hydroxytryptamine, dopamine and amino acids. Epilepsy Research 2005; 63(2-3):141-149
372. Leucht S, Kissling W, McGrath J, White P: Carbamazepine for schizophrenia. Cochrane Database of Systematic Reviews 2007(3):Art. No.: CD001258. DOI: 10.1002/14651858.CD001258.pub2
373. Harsing LG, Gacsalyi I, Szabo G, Schmidt E, Sziray N, Sebban C, Tesolin-Decros B, Matyus P, Egyed A, Spedding M, Levay G: The glycine transporter-1 inhibitors NFPS and Org 24461: a pharmacological study. Pharmacology Biochemistry and Behavior 2003; 74(4):811-825
374. Lane HY, Liu YC, Huang CL, Chang YC, Liau CH, Perng CH, Tsai GE: Sarcosine (N-Methylglycine) treatment for acute schizophrenia: A randomized, double-blind study. Biological Psychiatry 2008; 63(1):9-12

375. Tsai GC, Lane HY, Yang PC, Chong MY, Lange N: Glycine transporter I inhibitor, N-methylglycine (Sarcosine), added to antipsychotics for the treatment of schizophrenia. Biological Psychiatry 2004; 55(5):452-456
376. Lane HY, Huang CL, Wu PL, Liu YC, Chang YC, Lin PY, Chen PW, Tsai G: Glycine transporter I inhibitor, N-methylglycine (Sarcosine), added to clozapine for the treatment of schizophrenia. Biological Psychiatry 2006; 60(6):645-649
377. Neale JH, Olszewski RT, Gehl LM, Wroblewska B, Bzdega T: The neurotransmitter N-acetylaspartylglutamate in models of pain, ALS, diabetic neuropathy, CNS injury and schizophrenia. Trends in Pharmacological Sciences 2005; 26(9):477-484
378. Olszewski RT, Bukhari N, Zhou J, Kozikowski AP, Wroblewski JT, Shamimi-Noori S, Wroblewska B, Bzdega T, Vicini S, Barton FB, Neale JH: NAAG peptidase inhibition reduces locomotor activity and some stereotypes in the PCP model of schizophrenia via group II mGluR. Journal of Neurochemistry 2004; 89(4):876-885
379. Olszewski RT, Wegorzewska MM, Monteiro AC, Krolikowski KA, Zhou J, Kozikowski AP, Long K, Mastropaolo J, Deutsch SI, Neale JH: Phencyclidine and dizocilpine induced behaviors reduced by N-acetylaspartylglutamate peptidase inhibition via metabotropic glutamate receptors. Biological Psychiatry 2008; 63(1):86-91
380. Schoepp DD, Johnson BG, Wright RA, Salhoff CR, Mayne NG, Wu S, Cockerham SL, Burnett JP, Belegaje R, Bleakman D, Monn JA: LY354740 is a potent and highly selective group II metabotropic glutamate receptor agonist in cells expressing human glutamate receptors. Neuropharmacology 1997; 36(1):1-11
381. Krystal JH, Abi-Saab W, Perry E, D'Souza D, Liu NJ, Gueorguieva R, McDougall L, Hunsberger T, Belger A, Levine L, Breier A: Preliminary evidence of attenuation of the disruptive effects of the NMDA glutamate receptor antagonist, ketamine, on working memory by pretreatment with the group II metabotropic glutamate receptor agonist, LY354740, in healthy human subjects. Psychopharmacology 2005; 179(1):303-309
382. Patil ST, Zhang L, Martenyi F, Lowe SL, Jackson KA, Andreev BV, Avedisova AS, Bardenstein LM, Gurovich IY, Morozova MA, Mosolov SN, Neznanov NG, Reznik AM, Smulevich AB, Tochilov VA, Johnson BG, Monn JA, Schoepp DD: Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: a randomized Phase 2 clinical trial. Nature Medicine 2007; 13(9):1102-1107
383. Luby ED, Cohen BD, Domino EF, Rosenbaum G, Gottlieb JS: Model psychoses and schizophrenia. American Journal of Psychiatry 1962; 119(1):61-67
384. Kim JS, Kornhuber HH, Schmidburgk W, Holzmuller B: Low cerebrospinal fluid glutamate in schizophrenic patients and a new hypothesis on schizophrenia. Neuroscience Letters 1980; 20(3):379-382
385. Lodge D, Anis NA: Effects of phencyclidine on excitatory amino acid activation of spinal interneurones in the cat. European Journal of Pharmacology 1982; 77(2-3):203-204
386. Wachtel H, Turski L: Glutamate – A new target in schizophrenia. Trends in Pharmacological Sciences 1990; 11(6):219-220

387. Farber NB, Wozniak DF, Price MT, Labruyere J, Huss J, Peter HS, Olney JW: Age-specific neurotoxicity in the rat associated with NMDA receptor blockade: Potential relevance to schizophrenia? Biological Psychiatry 1995; 38(12):788-796
388. Olney JW, Farber NB: Glutamate Receptor Dysfunction and Schizophrenia. Archives of General Psychiatry 1995; 52(12):998-1007
389. Keshavan MS, Anderson S, Pettegrew JW: Is schizophrenia due to excessive synaptic pruning in the prefrontal cortex - The Feinberg hypothesis revisited. Journal of Psychiatric Research 1994; 28(3):239-265
390. Glantz LA, Lewis DA: Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. Archives of General Psychiatry 2000; 57(1):65-73
391. Selemon LD, Rajkowska G, Goldmanrakic PS: Abnormally high neuronal density in the schizophrenic cortex – A morphometric analysis of prefrontal area 9 and occipital area 17. Archives of General Psychiatry 1995; 52(10):805-818
392. Coyle JT: Substance use disorders and schizophrenia: A question of shared glutamatergic mechanisms. Neurotoxicity Research 2006; 10(3-4):221-233
393. Tamminga CA, Lahti AC, Medoff DR, Gao XM, Holcomb HH: Evaluating glutamatergic transmission in schizophrenia, in Glutamate and Disorders of Cognition and Motivation, vol 1003, 2003, pp 113-118
394. Lewis DA, Moghaddam B: Cognitive dysfunction in schizophrenia - Convergence of gamma-aminobutyric acid and glutamate alterations. Archives of Neurology 2006; 63(10):1372-1376
395. Abi-Saab WM, D'Souza DC, Moghaddam B, Krystal JH: The NMDA antagonist model for schizophrenia: Promise and pitfalls. Pharmacopsychiatry 1998; 31:104-109
396. Farber NB: The NMDA receptor hypofunction model of psychosis, in Glutamate and Disorders of Cognition and Motivation, vol 1003, 2003, pp 119-130
397. Glantz LA, Gilmore JH, Lieberman JA, Jarskog LF: Apoptotic mechanisms and the synaptic pathology of schizophrenia. Schizophrenia Research 2006; 81(1):47-63
398. Jarskog LF, Glantz LA, Gilmore JH, Lieberman JA: Apoptotic mechanisms in the pathophysiology of schizophrenia. Progress in Neuro-Psychopharmacology & Biological Psychiatry 2005; 29(5):846-858
399. Catts VS, Catts SV, McGrath JJ, Feron F, McLean D, Coulson EJ, Lutze-Mann LH: Apoptosis and schizophrenia: A pilot study based on dermal fibroblast cell lines. Schizophrenia Research 2006; 84(1):20-28
400. Castner SA, Goldman-Rakic PS: Long-lasting psychotomimetic consequences of repeated low-dose amphetamine exposure in rhesus monkeys. Neuropsychopharmacology 1999; 20(1):10-28
401. Selemon LD, Begovic A, Goldman-Rakic PS, Castner SA: Amphetamine sensitization alters dendritic morphology in prefrontal cortical pyramidal neurons in the non-human primate. Neuropsychopharmacology 2007; 32(4):919-931
402. Robinson TE, Kolb B: Alterations in the morphology of dendrites and dendritic spines in the nucleus accumbens and prefrontal cortex following repeated treatment with amphetamine or cocaine. European Journal of Neuroscience 1999; 11(5):1598-1604

403. Lipska BK: Using animal models to test a neurodevelopmental hypothesis of schizophrenia. Journal of Psychiatry & Neuroscience 2004; 29(4):282-286
404. Ozawa K, Hashimoto K, Kishimoto T, Shimizu E, Ishikura H, Iyo M: Immune activation during pregnancy in mice leads to dopaminergic hyperfunction and cognitive impairment in the offspring: A neurodevelopmental animal model of schizophrenia. Biological Psychiatry 2006; 59(6):546-554
405. Moore H, Jentsch JD, Ghajarnia M, Geyer MA, Grace AA: A neurobehavioral systems analysis of adult rats exposed to methylazoxymethanol acetate on E17: Implications for the neuropathology of schizophrenia. Biological Psychiatry 2006; 60(3):253-264
406. Paylor R, McIlwain KL, McAninch R, Nellis A, Yuva-Paylor LA, Baldini A, Lindsay EA: Mice deleted for the DiGeorge/velocardiofacial syndrome region show abnormal sensorimotor gating and learning and memory impairments. Human Molecular Genetics 2001; 10(23):2645-2650
407. Hikida T, Jaaro-Peled H, Seshadri S, Oishi K, Hookway C, Kong S, Wu D, Xue R, Andrade M, Tankou S, Mori S, Gallagher M, Ishizuka K, Pletnikov M, Kida S, Sawa A: Dominant-negative DISC1 transgenic mice display schizophrenia-associated phenotypes detected by measures translatable to humans. Proceedings of the National Academy of Sciences of the United States of America 2007; 104(36):14501-14506
408. Chen YJJ, Johnson MA, Lieberman MD, Goodchild RE, Schobel S, Lewandowski N, Rosoklija G, Liu RC, Gingrich JA, Small S, Moore H, Dwork AJ, Talmage DA, Role LW: Type III neuregulin-1 is required for normal sensorimotor gating, memory-related behaviors, and corticostriatal circuit components. Journal of Neuroscience 2008; 28(27):6872-6883
409. Segal DS, Geyer MA: Animal models of psychopathology, in Psychobiological foundations of clinical psychiatry. Edited by Judd LL, Groves PM. Philadelphia, JB Lippincott, 1985, pp 1-14

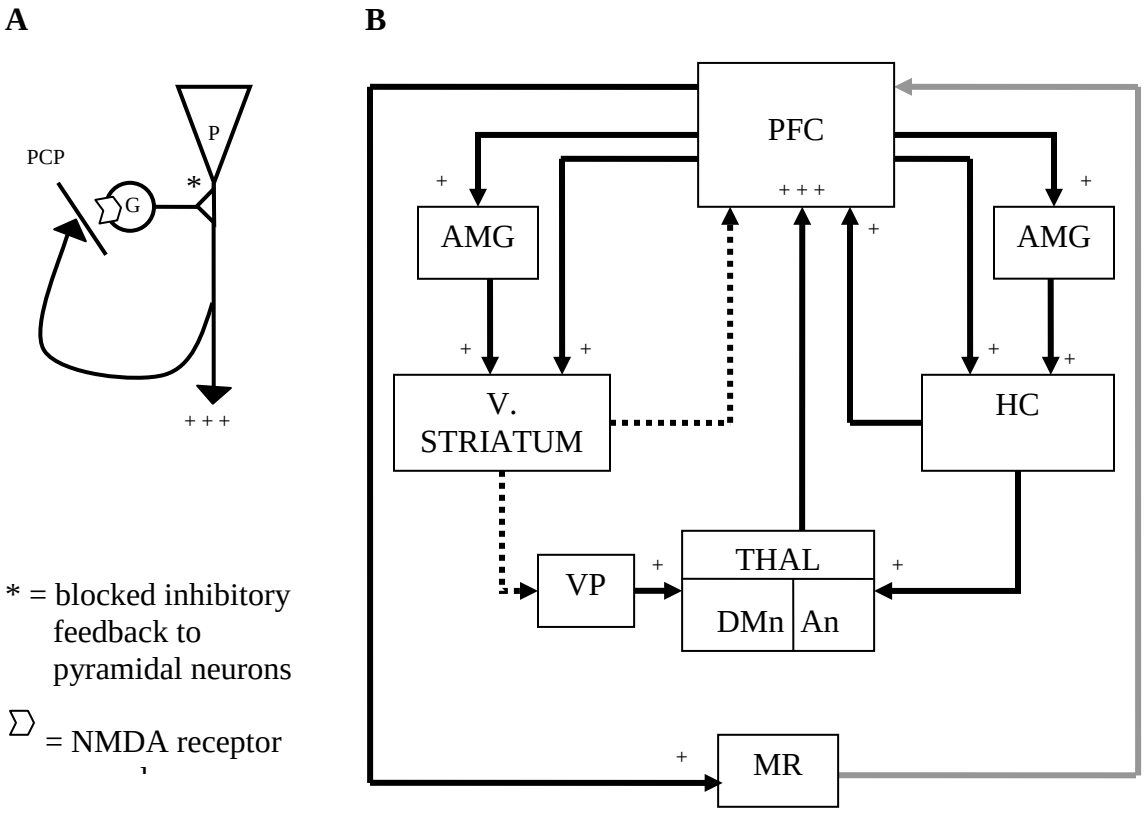

Figure 1.
Panel A: Site of action of PCP. G: GABAergic interneuron; P: pyramidal neuron.
Panel B: Circuits of the brain relevant to the PCP model of schizozphrenia.
Black unbroken lines indicate glutamatergic neurotransmission, the strength of which is indicated by the number of + signs.
Black dotted lines indicate dopaminergic neurotransmission.
Grey unbroken lines indicate serotonergic neurotransmission.
PFC: prefrontal cortex; AMG: amygdala; V. STRIATUM: ventral striatum; VP: ventral pallidum; THAL: thalamus; DMn: dorsomedial nucleus of thalamus; An: anterior nucleus of thalamus; HC: hippocampus; MR: median raphe.