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Themed Issue: Translational Neuropharmacology – Using Appropriate Animal Models to Guide Clinical Drug Development

REVIEW

Animal models of schizophrenia

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Developing reliable, predictive animal models for complex psychiatric disorders, such as schizophrenia, is essential to increase our understanding of the neurobiological basis of the disorder and for the development of novel drugs with improved therapeutic efficacy. All available animal models of schizophrenia fit into four different induction categories: developmental, drug-induced, lesion or genetic manipulation, and the best characterized examples of each type are reviewed herein. Most rodent models have behavioural phenotype changes that resemble 'positive-like' symptoms of schizophrenia, probably reflecting altered mesolimbic dopamine function, but fewer models also show altered social interaction, and learning and memory impairment, analogous to negative and cognitive symptoms of schizophrenia respectively. The negative and cognitive impairments in schizophrenia are resistant to treatment with current antipsychotics, even after remission of the psychosis, which limits their therapeutic efficacy. The MATRICS initiative developed a consensus on the core cognitive deficits of schizophrenic patients, and recommended a standardized test battery to evaluate them. More recently, work has begun to identify specific rodent behavioural tasks with translational relevance to specific cognitive domains affected in schizophrenia, and where available this review focuses on reporting the effect of current and potential antipsychotics on these tasks. The review also highlights the need to develop more comprehensive animal models that more adequately replicate deficits in negative and cognitive symptoms. Increasing information on the neurochemical and structural CNS changes accompanying each model will also help assess treatments that prevent the development of schizophrenia rather than treating the symptoms, another pivotal change required to enable new more effective therapeutic strategies to be developed.

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Abbreviations
5-HT_6, 5-hydroxytryptamine$_6$ receptor; BDNF, brain-derived neurotrophic factor; D_2, dopamine D_2 receptor; DISC-1, disrupted-in-schizophrenia 1; DTNBP1, dystobrevin-binding protein 1; EGF, epidermal growth factor; GAD_{65}, glutamic acid decarboxylase enzyme 65 kDa isoform; GAD_{67}, glutamic acid decarboxylase enzyme 67 kDa isoform; GAT-1, GABA transporter 1; GD, gestational day; GLAST, glutamate–aspartate transporter; Ig, immunoglobulin; LPS, lipopolysaccharide; MAM, methylazoxymethanol; NAA, *N*-acetylaspartic acid; nAcc, nucleus accumbens; NAAG, *N*-acetylaspartylglutamate; NGF, nerve growth factor; NMDA, *N*-methyl-D-aspartic acid; NRG1, neuregulin 1; PCP, phencyclidine; PFc, prefrontal cortex; PND, postnatal day; PPI, prepulse inhibition of acoustic startle; vHip, ventral hippocampal; VTA, ventral tegmental area

Introduction

Schizophrenia is a chronic debilitating neuropsychiatric disorder affecting approximately 1% of the population worldwide. Symptoms cluster into three categories: positive (including auditory and visual hallucinations, delusions, conceptual disorganization and thought disorder), negative (emotional blunting, social withdrawal, anhedonia, avolition, poverty of thought and content of speech) and cognitive dysfunction (including impaired executive function,

working memory and attention) (Andreasen, 1995). Patients present with extremely heterogeneous symptom combinations, making diagnosis and treatment problematic. Many patients undergo prolonged periods of remission interspersed with relapses of psychotic episodes. Disease onset is typically post adolescence (16–25 years), with a higher incidence of psychotic symptoms in males and a bimodal later onset (40–60 years) in females. Although the aetiology of schizophrenia remains contentious, it is a multifactorial neurodevelopmental disorder influenced by both genetic and environmental factors (Lewis and Lieberman, 2000; van Os *et al.*, 2010), such that monozygotic siblings of affected individuals show a 50–80% risk of developing the disorder.

The first drugs, found by serendipity rather than design in the 1950s, to treat the psychotic symptoms of schizophrenia (haloperidol and chlorpromazine, called classical neuroleptics) are also known as the first-generation antipsychotics. The second-generation or atypical antipsychotics, so called because of their different clinical profile (including clozapine, olanzepine, risperidone and aripiprazole) developed from the 1970s have less tendency to produce unwanted extrapyramidal side effects and hyperprolactinaemia (Remington, 2003). While first-generation antipsychotics are classified according to chemical structure, the second-generation antipsychotics are characterized according to their pharmacology. These drugs were developed to treat the positive (psychotic) symptoms and not the negative or cognitive impairments. However, multi-site, double-blind studies comparing several second-generation antipsychotics with a typical antipsychotic, perphenazine, failed to substantiate any major therapeutic advantage of the former (Lieberman *et al.*, 2005). The cognitive symptoms of schizophrenia often precede the occurrence of psychosis, and their treatment is considered a better predictor of therapeutic outcome (Mintz and Kopelowicz, 2007). However, while positive symptoms are currently treated to a varying degree by typical and atypical antipsychotics, the negative, and in particular, the cognitive impairments, remain resistant to treatment with current antipsychotics even after remission of the psychosis (Nuechterlein *et al.*, 2004; Keefe *et al.*, 2007; Mintz and Kopelowicz, 2007). Consequently, there is an urgent need to develop novel compounds that demonstrate increased efficacy against cognitive dysfunction and negative symptoms most likely by the use of adjunct therapy in combination with existing antipsychotics. In recognition of this problem, the US National Institute of Mental Health, in partnership with the US Food and Drug Administration and academic partners developed the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) and Treatment Units for Research on Neurocognition and Schizophrenia (TURNS) initiatives to attempt to establish a reliable, valid and consensus-derived method of assessing cognition, and improve the likelihood of successful development of new compounds that could be used alongside existing drugs to more effectively treat the cognitive and negative symptoms of schizophrenia (see http://www.MATRICS.ucla.edu and http://www.turns.ucla.edu). The MATRICS initiative identified seven core domains of cognition: working memory, attention/vigilance, reasoning and problem solving, processing speed, visual learning and memory, verbal learning and memory, and social cognition, that are deficient in schizophrenia which have to be treated to meet therapeutic needs, and recommended a specific neuropsychological test battery to characterize these domains. A development of this initiative is the evaluation of the clinical relevance and predictive value of existing preclinical cognitive tasks and agreement for the need to develop a preclinical cognitive test battery to aid drug development (Hagan and Jones, 2005; Nuechterlein *et al.*, 2005). Floresco *et al.* (2005) suggested using two approaches in experimental animals: lesions or drugs to manipulate specific systems altered in schizophrenia and developing models with cognitive deficits that resemble those seen in the disorder, to improve translational reliability of data obtained. Young *et al.* (2009) extensively reviewed existing animal cognitive paradigms and critically appraised their translational relevance to the seven human cognitive domains identified as being affected in schizophrenia. However, such cognitive paradigms need to be examined, not just in normal healthy animals, but in credible validated models of the disorder which will be reviewed in this paper.

Animal models of complex heterogeneous psychiatric disorders are clearly very valuable preclinical tools with which to investigate the neurobiological basis of the disorder. They offer a more rapid platform to monitor disease progression than in humans, and the opportunity to perform invasive monitoring of structural and molecular changes that underlie the cause of the disease and test novel therapeutics not possible in patients. However, a perplexing problem is how to assess some of the core symptoms of psychiatric disorders (like thoughts, and verbal learning and memory), which are uniquely human traits (Powell and Miyakawa, 2006). In general, most behaviours can only be indexed rather than directly quantified, and we are left to monitor performance in tasks designed to have translational relevance to core symptoms and make inference about the psychiatric state. A further problem with models of schizophrenia is that there is no current 'gold standard' medication available to treat all the symptoms that can be used as a definitive positive control in preclinical studies, although drugs like haloperidol and clozapine should reverse behavioural correlates of positive symptoms. Furthermore, many of the current antipsychotics may have a small therapeutic window of effect before sedation and other non-specific motor suppressant actions confound interpretation in tasks designed to assess negative and cognitive function (against which in any case these drugs have limited therapeutic effect).

All useful animal models should have the appropriate triad of face (symptom homology), construct (replicate the theoretical neurobiological rationale and pathology) and predictive (show the expected pharmacological response, or lack of it, to treatment by known antipsychotics and potential new adjunct therapies yet to be developed) validity to the clinical disorder being modelled. For schizophrenia, a suitable constellation of behavioural and neurochemical abnormalities would include postpubertal onset, loss of hippocampal and cortical connectivity and function, limbic dopamine dysregulation, cortical glutamatergic hypofunction, vulnerability to stress, abnormal response to reward, social withdrawal and cognitive impairment (Figure 1). Several recent articles (Floresco *et al.*, 2005; Hagan and Jones, 2005; Fone and Porkess, 2008; Millan and Brocco, 2008; Bellon *et al.*, 2009; Neill *et al.*, 2010) have reviewed individual animal models of schizophrenia or compared the potential

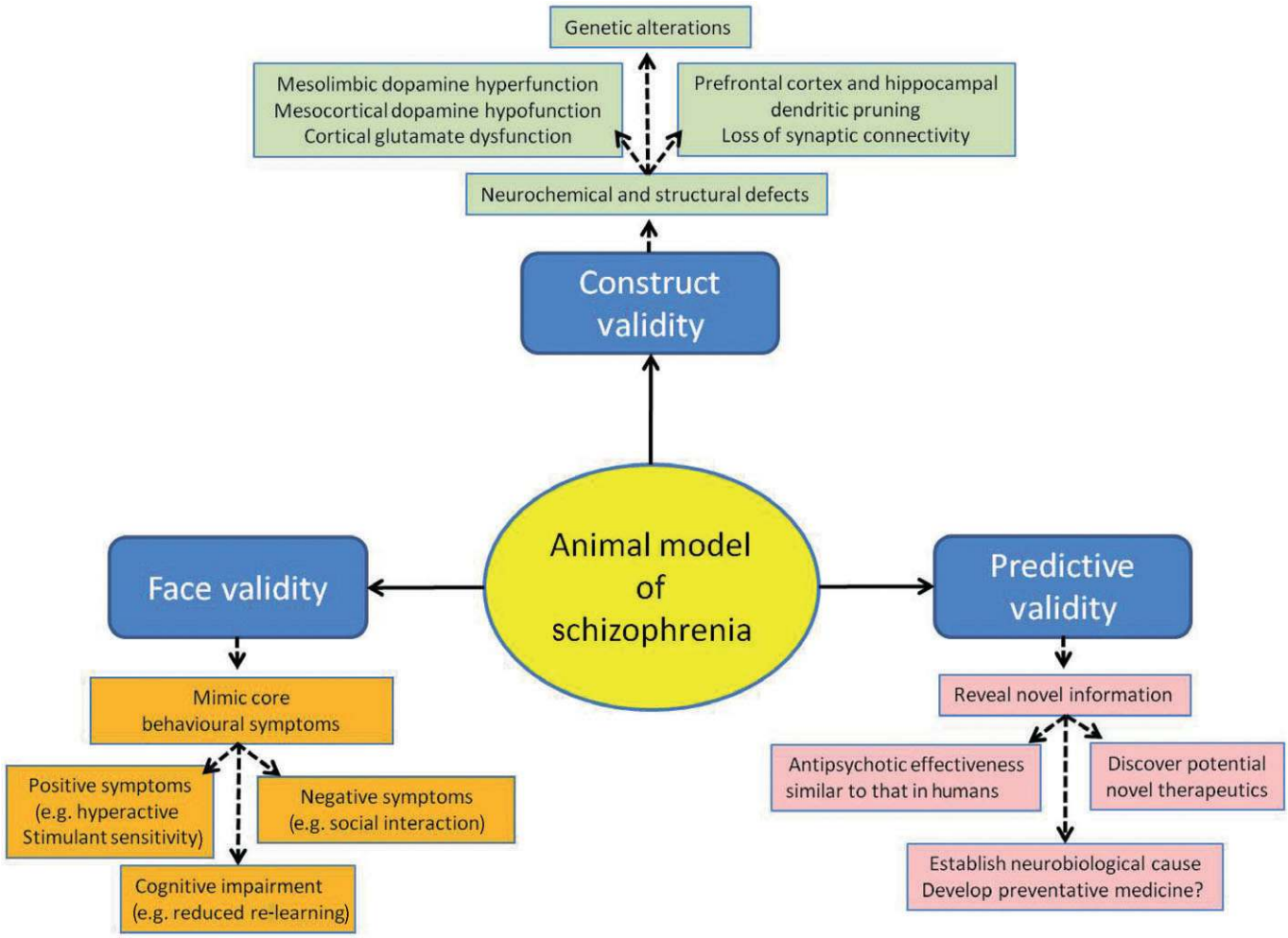

Figure 1

Schematic diagram of the key behavioural, neurochemical and structural changes expected be present and to have translational relevance to the three core symptom domains of schizophrenia in an animal model of the disorder.

application of some of the common models with emphasis on their predictive validity to evaluate novel compounds that could improve the cognitive and negative symptoms seen in schizophrenia.

Recently, it has been estimated that over 20 different animal models of schizophrenia have been developed (Carpenter and Koenig, 2008), although several have considerable overlap in the methodology/principle used, and all fit into four different induction categories: developmental, drug-induced, lesion or genetic manipulation, as will be discussed in this review. Initial animal models were developed on the basis of the tenet theory that dopamine dysfunction was central to the pathophysiology of schizophrenia, but with increased understanding of the genetic basis and potential involvement of glutamate animal models have also been developed to explore their involvement in the disorder. Most rodent models of schizophrenia tend to replicate aspects of the positive symptoms of schizophrenia (Table 1), such as hyperactivity probably reflecting enhanced mesolimbic dopamine function, but some, including methylazoxymethanol (MAM), neonatal hippocampal lesion, isolation rearing from weaning and chronic phencyclidine (PCP) administration, show cortical dopaminergic dysfunction and sensorimotor gating deficits that may be the consequence of altered development of frontal cortical–limbic circuits. Treatment of the negative and cognitive symptoms of schizophrenia is a vital and unmet clinical need that could have a major impact on patient recovery and re-integration into society. Therefore, the development of more comprehensive models that more adequately replicate deficits in these symptoms and help to understand causal factors is ongoing, but many of the models remain to be tested, as reviewed herein.

Neurodevelopmental models

Human epidemiology provides compelling evidence that exposure of the neonate, either during gestation or the perinatal period, to adverse environmental insults increases the risk of developing schizophrenia. Thus, maternal stress, malnutrition, infection or immune activation, or obstetric complications (such as hypoxia) during birth are just some of

Table 1

Comparative overview of the changes in basal and psychostimulant-induced locomotor activity in an open-field arena; sensorimotor gating; learning and memory; social interaction with a conspecific, structural and neurochemical changes in cortical and hippocampal areas and the reversal of these changes with antipsychotic and related drugs for selected animal models of schizophrenia

Animal model	Basal- and drug-induced locomotor activity	Sensorimotor gating	Cognition	Social interaction	Structure and neurochemistry	Antipsychotic reversal
Gestational MAM (GD17) (Moore *et al.*, 2006; Lodge *et al.*, 2009)	Spontaneous hyperactivity in novel arena emerging at puberty. Enhanced amphetamine- and NMDA antagonist-induced locomotion.	Deficit in PPI appears at puberty.	Normal acquisition, but impaired re-learning in the Morris water maze; impaired extra-dimensional shift in attentional set-shifting task	Reduced total social interaction appears prior to puberty.	Reduced PFc and hippocampal size, enlarged ventricals, reduced hippocampal soma size and neuropil; enhanced nAcc DA release; spontaneously hyperactive VTA DA neurones; decreased PFc parvalbumin GABA interneurones	No pharmacological reversal of behaviour attempted. CLZ does not reverse change in BDNF.
Post-weaning social isolation (Lapiz *et al.*, 2003; Fone and Porkess, 2008)	Hyperactivity in a novel arena appearing 2–3 weeks after commencing isolation; hyper-responsivity to amphetamine and cocaine together with increased nAcc DA release	Persistent, but strain-dependent reduction in PPI to acoustic startle appearing about 6 weeks after isolation	Deficit in novel object recognition; no effect on acquisition of spatial learning by impaired reversal learning in water maze, extra-dimensional shift in the attentional set-shifting task and fear-motivated conditioned emotional response	Increased aggression and increase in total social interaction	Reduced PFc volume; reduced dendritic spine density, cytoskeletal alteration and loss of parvalbumin-containing interneurones and reelin in the hippocampus; reduced PFc D_1 binding, no change in striatal D_2 density, but increased proportion of striatal D_2^{High}; increased spontaneously active VTA DA neurones	PPI reversed by atypical antipsychotics, D_2 antagonists, α_7-nicotinic agonists; novel object discrimination impairment reversed by 5-HT_6 antagonists and mGluR2/3 agonist
Amphetamine models (Featherstone *et al.*, 2007a; Featherstone *et al.*, 2008; Sarter *et al.*, 2009)	Sensitization of locomotor response to amphetamine	Persistent deficit in PPI dependent on dosage regimen	Deficits in attention and the attentional set-shifting task; hippocampal-dependent memory unimpaired	No reduction in social interaction	Enhanced mesolimbic DA response; altered ACh function in PFc	Locomotor sensitization blocked by CLZ and HLP; moderate attenuation of attention impairment by CLZ and HLP
PCP models (Jentsch and Roth, 1999; Phillips *et al.*, 2001; Mouri *et al.*, 2007; Neill *et al.*, 2010)	Sensitization of locomotor response to PCP; hyper-responsive locomotor response to amphetamine and mild stress	No sustained deficit in PPI	Deficits in novel object recognition, attentional set shifting and T-maze delayed alternation	Reduced frequency and duration of primate social behaviour	Reduced basal and stress-induced PFc DA and glutamate release; decreased synaptic spines on Fc neurones and cortical and hippocampal parvalbumin-positive neurones	Deficits in reversal learning reversed by atypical antipsychotics but not HLP; locomotor sensitization attenuated by CLZ and HLP

Table 1

Continued

Animal model	Basal- and drug-induced locomotor activity	Sensorimotor gating	Cognition	Social interaction	Structure and neurochemistry	Antipsychotic reversal
Neonatal ventral hippocampal lesion (Lipska, 2004; Tseng *et al.*, 2009)	Locomotor hyper-responsivity to stress, amphetamine and NMDA receptor antagonists; enhanced apomorphine-induced stereotypy	Adult onset deficit in PPI	Impaired acquisition of T-maze delayed alternation and water maze; impaired radial arm maze choice accuracy; selective deficit in extra-dimensional shift and reversal in the attentional set-shifting task	Deficits in social interaction with increased aggression at all developmental ages	Unaltered basal nAcc DA release, but enhanced response to stress or amphetamine; reduced mPFc NAA levels and GAD_{67} mRNA expression	Amphetamine-induced hyperactivity reversed by acute or chronic antipsychotic injection; social interaction deficit not reversed by CLZ
DISC-1 knock-out (Jaaro-Peled, 2009)	Hyperactivity seen in L100P, CaMK-ΔC mutants, but not in others; no data available regarding psychostimulant-induced locomotor activity to date	Deficits in PPI seen in some (e.g. constitutive CaMK-ΔC, L100P, Q31L), but not all mutants (e.g. inducible CaMK-ΔC, Δ25 bp); PPI not tested in CaMK cc or BAC ΔC mutants	Impaired T-maze performance seen in most strains; impaired spatial working memory only seen in female CaMK-ΔC inducible mutants	Reductions in social activity seen in some strains (e.g. Q31L) and some CaMK- ΔC transgenics	Reduced brain volume in most strains; enlarged lateral ventricles, reduced hippocampal and PFc dendritic density, structure and complexity in some strains; reduced hippocampal parvalbumin immunoreactivity in some, but not all mutants	PPI deficits in L100P mice reversed by HLP and CLZ
Neuregulin1 and ErbB4 knock-out (Harrison and Law, 2006a; Mei and Xiong, 2008)	Most, but not all, neuregulin and ErbB4 mutants show spontaneous locomotor hyperactivity, but inconsistent responses to psychostimulants	PPI deficits seen in most neuregulin mutants reviewed; ErbB4 mutants show normal PPI	Impaired contextual fear and mismatched negativity performance in some mutants	Some deficits in social interaction, increased aggression and reduced responses to social novelty	Increased lateral ventricles and reduced hippocampal spine density; reduction in functional forebrain NMDA receptors	Spontaneous and psychostimulant-induced locomotor hyperactivity reversed by CLZ in $Nrg1(\Delta TM)^{+/-}$ and $Nrg1(BACE)^{-/-}$ mutants
Dysbindin knock-out (Karlsgodt *et al.*, 2011; Papaleo *et al.*, 2010)	Spontaneous locomotor hyperactivity and hyper-responsivity to amphetamine challenge	Increased PPI and startle response shown to be reversed by quinpirole, but not eticlopride	Increased acquisition of T-maze task; impaired spatial reference memory and novel object recognition performance	Reduced social contact during social interaction task	Hyperexcitability of PFc pyramidal neurones; altered synaptic structure and formation; elevated HVA/DA ratio in cortico-limbic regions	No data on antipsychotic reversal
Reelin knock-out (Krueger *et al.*, 2006; Tueting *et al.*, 2006)	Reduced locomotion in an open field; enhanced response to methamphetamine	Variable PPI responses, highly dependent on strain, environment and testing protocol	Few memory deficits reported; normal reversal learning and inhibitory control, normal MWM performance; some learning deficits in acquisition of operant tasks	Some modulation of social activity in novelty and/or interaction tasks	Increased neuronal packing and decreased dendritic spine density in PFc and hippocampal neurones	Normalization of reduced spontaneous activity by OLZ

Note that some of the tasks as discussed in the review are thought to have translational relevance to particular symptom domains affected in schizophrenia. However, other experimental observations, such as drug-induced changes, do not directly relate to core symptoms, but are used as an index to test dysfunction of the neuronal pathways that are thought to contribute to schizophrenia. $5\text{-}HT_6$, 5-hydroxytryptamine$_6$ receptor; BDNF, brain-derived neurotrophic factor; CLZ, clozapine; D_1, dopamine D_1 receptor; D_2, dopamine D_2 receptor; DA, dopamine; DISC-1, disrupted-in-schizophrenia 1; GAD_{67}, glutamic acid decarboxylase enzyme 67 kDa isoform; HLP, haloperidol; MWM, Morris water maze; PFc, prefrontal cortex; PPI, prepulse inhibition of acoustic startle; NAA, *N*-acetylaspartic acid; nAcc, nucleus accumbens; NMDA, *N*-methyl-D-aspartic acid; OLZ, olanzapine; PCP, phencyclidine; VTA, ventral tegmental area.

the diverse perturbations that increase the risk of developing schizophrenia, consistent with it having a neurodevelopmental origin (Lewis and Levitt, 2002). A favoured current working hypothesis is that exposure of individuals with a genetic predisposition to an early-life adverse event could trigger an altered pattern of neuronal development and connectivity that subsequently results in the expression of a schizophrenic phenotype. While the precise nature of the early-life adverse event may not be critical, the time that this occurs is. Developmental animal models of schizophrenia utilize manipulations of environment, or drug administration during the sensitive perinatal period, to produce irreversible changes in CNS development. Disruption of neurogenesis during a critical gestational period, neonatal ventral hippocampal lesions, post-weaning social isolation of rodents and perinatal or maternal immune activation have all been proposed as neurodevelopmental models that replicate several of the core symptoms of schizophrenia. Consistent with their face validity, the long-term behavioural changes typically appear post-puberty, replicating the chronology of symptomology seen in schizophrenia.

Gestational MAM

MAM, naturally occurring in the seeds of cycad plants, is an anti-mitotic (and anti-proliferative) agent that methylates DNA (Matsumot and Higa, 1966) and specifically targets neuroblast proliferation in the CNS without affecting glial cells or causing teratogenic effects in peripheral organs (Cattabeni and DiLuca, 1997). Treatment of pregnant rat dams with MAM does not affect litter size or pup body weight (Balduini *et al.*, 1991b; Flagstad *et al.*, 2004), but selectively affects brain development. Indeed, administration of MAM to pregnant rat dams affects those brain structures undergoing the most rapid development in the fetus, producing long-lasting anatomical and behavioural deficits in the offspring (Moore *et al.*, 2006; Lodge and Grace, 2009), which are dependent on the precise gestational day (GD) of administration (Talamini *et al.*, 1998; 2000; Fiore *et al.*, 1999). Cortical neurogenesis is at its peak during GD15 in the rat, and disruption of this process causes a marked decrease in cell number (Bayer and Altman, 1995). Thus, when administered on GD15, MAM decreases whole brain cerebellar and hippocampal volume as measured by high-field MRI (Johnson *et al.*, 2006), and causes gross morphological changes, including microcephaly and profound cortical dysplasias, decreasing cortical mass by up to 70% (Cattabeni *et al.*, 1989), which is much more profound than the features typically observed of schizophrenia (Shenton *et al.*, 2001). In contrast, MAM administration on GD17, when cortical cell proliferation is much reduced, results in a more restricted preferential size reduction in neocortical and limbic structures, including the medial prefrontal (PFc), entorhinal and occipital cortices and the hippocampus, and increased neuronal density in the perirhinal cortex (Moore *et al.*, 2006; Matricon *et al.*, 2010). A careful immunohistochemical analysis has shown a specific reduction in neuronal number in the CA2 subfield of the hippocampus, but reduced soma size and neuropil, without cell loss, in other subfields (Matricon *et al.*, 2010). However, ventricular enlargement (one of the more consistent findings in schizophrenia) is less consistent in GD17 MAM rat pups and does not reach significance (Matricon *et al.*, 2010).

Likewise, the behavioural alterations seen in MAM offspring vary according to the GD of MAM administration in a sequential manner: GD14 increases exploration, GD15 causes nocturnal hyperactivity, while GD16 and 17 decrease activity, which could reflect a switch from destruction of striatal cholinergic to dopaminergic neurones from GD14 to 17 treatment (Balduini *et al.*, 1991a), the latter being more similar to changes seen in schizophrenia. Furthermore, the extent of motor impairment in the rotorod test progressively reduces with increase in GD age of MAM treatment (Balduini *et al.*, 1991b), and only >GD17 administration reduced active avoidance in a shuttle box (Balduini *et al.*, 1991a), suggesting impaired acquisition of learning occurs with later administration times (Balduini *et al.*, 1991a; Fiore *et al.*, 1999). The observation of disorganization, sporadic density and heterotopias within the pyramidal CA3 region of the hippocampus with GD17, but not GD15 administration, which has also be observed in schizophrenia patients, lends weight to the use of GD17 MAM exposure as a preclinical model for schizophrenia (Moore *et al.*, 2006). Interestingly, GD17 MAM offspring show reduced nerve growth factor (NGF) and brain-derived nerve growth factor (BDNF) in the parietal cortex at adulthood (Fiore *et al.*, 2004), but whether this is a cause or consequence of the neurodevelopmental changes observed is unclear. Similarly, both an increase and a decrease in BDNF levels have been reported in schizophrenic patients, so the relevance of this observation to the disorder is unclear (Takahashi *et al.*, 2000; Shoval and Weizman, 2005).

Thus, not only does GD17 MAM produce a pattern of histopathology similar to that observed in schizophrenia, but also behavioural abnormalities with more specific translational homology to dysfunction of the frontal cortex and limbic dopaminergic inputs (Jongen-Relo *et al.*, 2004; Moore *et al.*, 2006) accompanied by increased neural density rather than neuronal loss. Specifically, GD17 MAM reduces the thickness of the hippocampus, thalamus and several cortical regions, as well as decreasing total brain weight by approximately 11%, without producing striatal cell loss (Flagstad *et al.*, 2004). GD17 MAM also enhances the locomotor response to amphetamine (Moore *et al.*, 2006), and increases microdialysate dopamine release in the nucleus accumbens (nAcc), but not the frontal cortex (Flagstad *et al.*, 2004), consistent with the production of a hyperactive subcortical dopamine system thought to contribute to psychosis in humans. Elegant electrophysiological studies by the Grace research group has shown that the spontaneous firing rate of ventral tegmental area (VTA) dopamine neurones is enhanced in GD17 MAM rats, which like the augmented amphetamine-induced locomotion is reversed by inactivation of the ventral hippocampus (Lodge and Grace, 2007). Indeed, these workers suggest that the hyperactivity of VTA dopamine neurones may result from hyperactivity of neurones in the ventral subiculum of the hippocampus (Lodge and Grace, 2008; Lodge *et al.*, 2009), which in turn may be the consequence of MAM causing a loss of parvalbumin-containing GABAergic interneurones in this area (Penschuck *et al.*, 2006), another neurochemical feature seen in schizophrenia (Beasley *et al.*, 2002; Guidotti *et al.*, 2005). GD17 MAM-treated rats also exhibit a spontaneous hyperactivity when placed in a novel arena that only emerges at puberty, and have enhanced sensitivity to the *N*-methyl-D-aspartic

acid (NMDA) receptor antagonist, dizolcipine (MK-801) which thus causes a greater hyperactivity than seen in controls (Le Pen *et al.*, 2006). PCP-induced orofacial dyskinesias (thought to be an index of frontocortical lesions) were also enhanced in GD17 MAM offspring (Moore *et al.*, 2006). Although not unique to schizophrenia, impaired prepulse inhibition of the acoustic startle (PPI) response occurs in this disorder (Braff *et al.*, 2001), and the high cross-species neurobiological homology of the reflex has resulted in this becoming a common test to validate rodent models (Swerdlow *et al.*, 2000; Geyer *et al.*, 2001). PPI is thought to reflect the sensorimotor gating process that occurs in the first few hundred milliseconds prior to conscious attention, filtering out weak and unimportant stimuli during a sensory task, and is therefore, thought to reflect pre-attention processing (Young *et al.*, 2009). Most groups report that PPI is also impaired in GD17, but not GD15 MAM rat pups (Moore *et al.*, 2006; Hazane *et al.*, 2009) (although others only find PPI impairment with MAM injection on GD10 or 11 Talamini *et al.*, 2000), and like the enhanced locomotor activity to a novel arena, the PPI deficit shows age-dependent development (Le Pen *et al.*, 2006; Hazane *et al.*, 2009).

Several studies have attempted to characterize the cognitive changes that occur in MAM offspring, but many of these have been conducted in GD15 rather than GD17 MAM rats and when this is taken into account results are less consistent. Several studies have failed to show alteration in cognitive paradigms when MAM is administered up to GD15; such as lack of change in fear-conditioned freezing or two-way active avoidance behaviour (Jongen-Relo *et al.*, 2004), a form of associative learning which is impaired in schizophrenia (Rushe *et al.*, 1999). In a food-motivated alternating Y-maze paradigm (thought to represent spatial working memory which is impaired in schizophrenia, Park and Holzman, 1992) GD17 MAM rats learned the initial rule more quickly than the controls, but took more trials to attain rule reversal (Moore *et al.*, 2006). While in a spatial recognition Y-maze task, where the third arm is only available on the second trial, GD17 MAM offspring failed to show the normal control preference for the novel arm at post-puberty (>PND60) and not when pre-pubertal (Le Pen *et al.*, 2006; Hazane *et al.*, 2009). In an eight-arm radial arm maze while GD15 MAM offspring could not learn the rule, GD17 offspring were able to learn the task, but were impaired in this hippocampal-dependent spatial working memory task with the introduction of a 30 min delay between baiting the first and second four arms (Gourevitch *et al.*, 2004), consistent with impairment of prefrontal cortical–hippocampal connectivity. In contrast, in the Morris water maze (thought to map to the visual learning and memory domain in humans), GD15 MAM offspring (of both genders) were able to acquire the location of a hidden platform in a fixed position as well as controls, but took longer to re-learn a new fixed platform location, suggesting that it may have produced behavioural rigidity. In another study, GD17 MAM offspring showed impairment in acquisition to find a fixed platform position in the Morris water maze (Hazane *et al.*, 2009), but reversal learning was not examined. GD17 MAM Sprague-Dawley rats took significantly more trials to reach criterion on the extra-dimensional shift and reversal trials (Featherstone *et al.*, 2007b) in the attentional set-shifting task (thought to be a rodent analogue of the Wincosin card sorting task that maps to the reasoning and problem-solving cognitive domain and was identified by the TURNS initiative as useful to determine problem-solving deficits) (Birrell and Brown, 2000), consistent with the known effect of MAM on the parietal cortex and/or PFc, which are involved in this response. In contrast, in the five-choice serial reaction test of attention processing (thought to map to the attention and speed of processing cognitive domain in humans), rats receiving the same treatment regimen failed to show a difference in any parameter (e.g. accuracy, premature responding, omissions. . . .) from controls (Featherstone *et al.*, 2007b), suggesting that MAM may not affect sustained attention even though this is also dependent on PFc function. Very few studies have examined neurotransmitter release in the MAM model. Early studies showed that both basal and potassium-induced glutamate release from hippocampal synaptosomes was elevated (without concomitant alteration in GABA) in GD15 MAM-treated rat offspring (DiLuca *et al.*, 1997), which could contribute to the change in long-term potentiation and cognition observed in these rats. Similar elevated levels of glutamate have been found in the PFc and hippocampus of patients with schizophrenia (van Elst *et al.*, 2005). Although decreased reelin hypermethylation (discussed further in the genetics section later) and expression have been associated with schizophrenia, these effects do not appear to be replicated in the whole hippocampus of GD17 MAM rats (Matricon *et al.*, 2010).

The general consensus is that MAM administration at or before GD15 produces too widespread a disruption of brain morphology and behaviour to provide a useful model of changes seen in schizophrenia and that GD17 MAM is the optimal strategy. However, the effects may be very dependent on rat strain. As the effects of MAM are critically dependent on the GD of treatment, the usual practice of monitoring a vaginal plug to determine conception and calculate the MAM treatment day is inaccurate and may result in considerable variation in the resultant neurodevelopmental changes produced. The MAM model appears to have reasonable face validity for positive and cognitive symptoms, and has construct validity in terms of structural and dopaminergic changes observed. Surprisingly, few behavioural studies have been performed to carefully evaluate the GD17 model, and no studies have used pharmacological agents to attempt to reverse any of these behaviours, so the predictive validity of this paradigm to detect existing antipsychotic drugs or novel pro-cognitive compounds that might be useful to treat schizophrenia is unknown. In the only study to attempt to modify MAM-induced effects (GD12 MAM 20 $mg \cdot kg^{-1}$) with antipsychotics, neither clozapine (20 $mg \cdot kg^{-1}$) nor haloperidol (2 $mg \cdot kg^{-1}$ once per day i.p. for 8 days from PND28) reversed the changes in hippocampal, striatal or entorhinal cortex BDNF or NGF levels measured by Western blots, although some complex interactions were observed (Fiore *et al.*, 2008). Similar neurochemical observation can only be made in post-mortem tissue usually following long-term antipsychotic medication, so it is difficult to evaluate the clinical relevance of such findings.

Post-weaning social isolation

Within a colony, rats display a defined social structure and develop a hierarchy that plays a critical impact on their

development. Thus, social deprivation of rat pups from the age of weaning (by placing them in separate cages from littermates) alters brain development and causes behavioural deficits at adulthood (Lapiz *et al.*, 2003; Fone and Porkess, 2008), which are unaltered by social re-integration in later life (Pascual *et al.*, 2006). For instance, post-weaning social isolation of rodents induces spontaneous locomotor hyperactivity, enhanced responses to novelty (neophobia), sensorimotor gating deficits, cognitive impairments, and heightened anxiety states and aggression (Valzelli, 1973; Einon and Morgan, 1977; Heidbreder *et al.*, 2000; Weiss *et al.*, 2004; Fone and Porkess, 2008; Marsden *et al.*, 2011). Collectively, these behavioural changes have been termed the 'isolation syndrome', and several of these features resemble some of the core symptoms of schizophrenia. Where available, this review reports behaviours where reversal with current antipsychotic drugs or potential pro-cognitive adjunct therapeutic agents has been utilized, so that the predictive validity of the paradigm can be evaluated.

Isolation-reared rats are consistently more active than group-housed littermates when placed in a mildly aversive novel arena (Fone *et al.*, 1996; Dalley *et al.*, 2002; Silva-Gomez *et al.*, 2003; Del Arco *et al.*, 2004). This hyperactivity is typically expressed as increased horizontal activity and rears particularly evident after the first 15 min in the arena, suggesting an inability to habituate, which probably reflects mesolimbic dopamine hyperactivity (as discussed later) and may serve as an index for the positive symptoms in schizophrenia. Although hyperactivity appears within 2–3 weeks of commencing isolation (Bakshi and Geyer, 1999) is easily measured, relatively robust and well sustained with repeated testing (Hall *et al.*, 1998a; Fabricius *et al.*, 2010a), few groups have examined the sensitivity of this behaviour to drugs used to treat schizophrenia. A recent study has shown that the isolation-induced hyperactivity is reduced by the preferential dopamine D_3 receptor antagonists, S33084 and S33138, and less markedly by the D_2 receptor antagonist, L741 626, none of which attenuate activity in group-housed controls (Watson *et al.*, 2011). In addition, the known antipsychotics haloperidol, olanzapine, risperidone and the putative anti-schizophrenia agent and mGluR2/3 agonist, LY404039, and its analogue, LY379268, also reverse isolation-induced hyperactivity (Fabricius *et al.*, 2010a; Jones *et al.*, 2011) as does addition of the NMDA receptor modulator, L-serine [which is reduced in cerebrospinal fluid in schizophrenia (Bendikov *et al.*, 2007)], to the drinking water (Shigemi *et al.*, 2010). Given the clinical propensity of existing antipsychotic drugs to reverse positive symptoms (Patil *et al.*, 2007) and that isolation-induced locomotor hyperactivity results from mesolimbic dopamine hyperactivity, this behavioural test may be a useful model with high predictive validity to test drug reversal of the positive symptoms of schizophrenia.

Isolation-reared rats consistently show impaired PPI of acoustic startle compared to group-housed controls, thought to reflect sensorimotor gating deficits (Varty *et al.*, 1999; Cilia *et al.*, 2001; 2005b; Schubert *et al.*, 2009). Although this phenomenon is strain dependent (Varty and Geyer, 1998), it gradually appears with development (Bakshi and Geyer, 1999; Cassidy *et al.*, 2010a), and it was this observation that led to the proposal that this could be a developmental model of schizophrenia (Geyer *et al.*, 1993). Once established, the isolation-induced PPI deficit persists for weeks over multiple tests (Cilia *et al.*, 2001; Weiss and Feldon, 2001) and is restored, or at least partially reversed, by acute injection of the atypical antipsychotics, quetiapine, olanzapine, clozapine and risperidone (Wilkinson *et al.*, 1994; Varty and Higgins, 1995; Bakshi *et al.*, 1998; Cilia *et al.*, 2001); the dopamine D_2 receptor antagonist, raclopride (Geyer *et al.*, 1993); α7nicotinic receptor agonists (Cilia *et al.*, 2005a); and the 5-HT_{2A} receptor antagonist, M100907 (volinanserin) (Geyer *et al.*, 1999). Furthermore, bilateral injection of the neurotoxin, 6-hydroxydopamine to deplete dopamine into the nAcc also attenuates the PPI deficit seen in isolates (Powell *et al.*, 2003), consistent with this involving hyperactivity in the mesolimbic dopamine system. On a cautionary note, several of these compounds, such as the 5-HT_{2A} antagonist, volinanserin, only showed modest efficacy in acute clinical trials, which was not as good as haloperidol (Gray and Roth, 2007); the atypical antipsychotic, iloperidone, failed to reverse isolation-induced PPI deficits (Barr *et al.*, 2006); and the mGluR2/3 agonist, LY379268, further impaired PPI deficits in isolates (Jones *et al.*, 2011). However, the ability of antipsychotics to reverse PPI deficits in patients with schizophrenia is also inconsistent (see reviews by Braff *et al.*, 2001; Hagan and Jones, 2005). Several clinical reports have found both typical and atypical antipsychotics improve PPI deficits in patients responsive to treatment. Yet, in drug-free first-episode schizophrenic patients, neither the typical antipsychotic, zuclopenthixolor, nor the atypical antipsychotic, risperidone, had any effect (Mackeprang *et al.*, 2002), and compared to unmedicated controls, neither olanzapine nor haloperidol treatment produce any significant improvement in PPI (Duncan *et al.*, 2003). So, the predictive reliability of using this test alone is clearly questionable.

Humans and rodents alike have an innate curiosity to preferentially explore novel over familiar objects, and assessment of this differential exploration forms the basis of the novel object recognition task, which is thought to assess visual episodic memory (Dere *et al.*, 2007; Winters *et al.*, 2008) and to map in a translational manner to the visual learning and memory domain affected in schizophrenia (Young *et al.*, 2009). In the classic two-trial novel object recognition task, several groups have shown that both male and female isolation-reared rats show premature time delay-induced forgetting, so that they are unable to discriminate between novel and familiar objects in the second-choice trial typically after a 2 h inter-trial interval (Bianchi *et al.*, 2006; King *et al.*, 2009; McLean *et al.*, 2010a; Marsden *et al.*, 2011). The impairment in object recognition is likely to reflect deficits in recognition memory, rather than cognitive inflexibility reducing attention to the new stimulus as has been suggested by some, given that no impairment in novel object discrimination occurs in isolation-reared rats using short inter-trial intervals such as 1–15 min (Lapiz *et al.*, 2000; McLean *et al.*, 2010a). Recently, some studies have shown the ability of 5-HT_6 receptor antagonists (King *et al.*, 2007), dopamine D_3 receptor antagonists (Watson *et al.*, 2011) and mGluR2/3 agonists (Jones *et al.*, 2011) to reverse isolation-induced deficits in object recognition, so this could be a very promising behavioural task to help predictive evaluation of potential novel pro-cognitive drugs for use as adjuncts to antipsychotics (Marsden *et al.*, 2011), but whether this will translate to

their ability to reverse cognitive deficits in schizophrenia is unknown.

Most studies find that isolation rearing does not affect the rate of acquisition in visuo-spatial learning tasks such as the rotating T-maze (Li *et al.*, 2007a) or Morris water maze in rats (Schrijver *et al.*, 2002; Quan *et al.*, 2010) or mice (Ibi *et al.*, 2008), thought to map to visual learning and memory cognitive domain impaired in schizophrenia. Although one group found increased retention (Lapiz *et al.*, 2001) in learning a fixed location platform position in the water maze, most studies find impaired retention or persistence of spatial memory (Quan *et al.*, 2010). Furthermore, isolation rearing appears to impair cognitive flexibility in reversal learning tasks (Schrijver *et al.*, 2004; Li *et al.*, 2007a), and this deficit is accompanied by alteration in long-term potentiation both in the hippocampus (Ibi *et al.*, 2008) and in the PFc (Quan *et al.*, 2010). Isolates may also be preferentially impaired in tasks thought to be relevant to executive function that require shifting from spatial to non-spatial cues (Schrijver and Wurbel, 2001), and in the extra-dimensional shift in the attentional set-shifting task (McLean *et al.*, 2010a) thought to have translational relevance to the reasoning and problem-solving cognitive domain affected in schizophrenic patients. Indeed, in an analogous manner, schizophrenic patients exhibit a selective deficit in the extra-dimensional shift of the Wisconsin card sorting task (Tyson *et al.*, 2004; Jazbec *et al.*, 2007). While spatial learning and acquisition are highly dependent on hippocampal–neocortical pathways, performing an attentional shift to learn a new rule depends primarily on PFc–striatal pathways, which would appear to be preferentially affected by social isolation from weaning (Quan *et al.*, 2010). Unfortunately, few studies have examined whether antipsychotics can reverse any of these cognitive impairments, although chronic clozapine administration restored the reversal learning deficit in the T-maze task (Li *et al.*, 2007a), a finding that questions the predictive validity of the model for cognitive symptoms given the notorious poor efficacy of current antipsychotics to perform this in the clinic. Alterations in catecholaminergic neurotransmission in mesolimbic and other brain regions are thought to underlie many of the behavioural changes induced by isolation rearing (Fulford and Marsden, 1998a,b; 2007; Hall *et al.*, 1998b; Lapiz *et al.*, 2003; Fone and Porkess, 2008). Similar to changes thought to occur in schizophrenia, both *in vivo* and *ex vivo* studies on isolates show increased dopamine turnover in the amygdala and nAcc, and decreased turnover in the infralimbic PFc (Jones *et al.*, 1992; Hall *et al.*, 1998b; Fone and Porkess, 2008). Isolates also show enhanced PFc dopamine release in response to olanzapine and clozapine, but not haloperidol (Heidbreder *et al.*, 2001) and an increased number of spontaneously active neurones with a more irregular bursting firing pattern in the VTA (Fabricius *et al.*, 2010b). While some changes in glutamate and amino acid release and turnover have been reported (Melendez *et al.*, 2004), these still remain relatively unexplored and further work on the construct validity of the findings is required.

Several of the neurobiological changes in the brain of isolation-reared rats resemble those seen in the schizophrenic patient, hence the model has good construct validity. For example, as in schizophrenic patients (Hirayasu *et al.*, 2001; Harrison, 2004), a selective reduction in PFc volume occurs in isolation-reared rats (Day-Wilson *et al.*, 2006; Schubert *et al.*, 2009) accompanied by decreased dendritic spine density and morphology (Silva-Gomez *et al.*, 2003; Pascual and Zamora-Leon, 2007), cytoskeletal alterations (Bianchi *et al.*, 2006) and reduced parvalbumin and calbindin-containing GABAergic chandelier cartridges (Harte *et al.*, 2007; Bloomfield *et al.*, 2008) of hippocampal and PFc interneurones. The age of commencing isolation rearing and gender both interact to affect the extent of change in dendritic spine morphology and complexity that develops in PFc, anterior cingulate and orbitofrontal cortices (Ferdman *et al.*, 2007). A micro-array gene expression study in the PFc supports the idea that altered synaptic connectivity occurs in isolation-reared rats, as several genes involved in glutamatergic signalling, apoptosis, cell differentiation and some immediate early genes, including c-Fos, Arc, NGF1-B, Erg4 and Erg2, are all down-regulated (Levine *et al.*, 2007).

Reelin is an extracellular matrix protein secreted by cortical GABAergic neurones in both rodents and humans, thought to be involved in synaptic formation, stability and plasticity, and has been associated with cognitive impairment in patients (Guidotti *et al.*, 2005). Furthermore, both reelin mRNA and GAD67 mRNA expression have been found to be significantly decreased in GABAergic interneurones in the superficial layers of the PFc in patients with schizophrenia (Guidotti *et al.*, 2000). Unfortunately, changes in post-mortem tissue from schizophrenic patients tell us little about any potential developmental role the protein may have in the disorder. Interestingly, reelin is also reduced in the ventral dentate gyrus of the hippocampus in isolation-reared rats to an extent that correlates with impairment in conditioned avoidance learning (Cassidy *et al.*, 2010b). Furthermore, increased expression of reelin-immunoreactive cells in layer 1 of the PFc occurs at the same time ~PND60 as the emergence of PPI deficits in isolates, which may be linked with synaptic remodelling in this area at this age (Cassidy *et al.*, 2010a).

In addition to the structural changes, isolation rearing induces several receptor changes relevant to observations in schizophrenia. Isolates have reduced PFc dopamine D_1 receptor density (Toua *et al.*, 2010), a change which has been reported to correlate with cognitive deficits in schizophrenia (Goldman-Rakic *et al.*, 2004; Scott and Aperia, 2009). However, changes in mesolimbic dopamine D_2 receptor expression are inconsistent; down-regulation in striatum (Hall *et al.*, 1998b), but no change in mesolimbic (Del Arco *et al.*, 2004), hippocampal, PFc or amygdala areas (Malone *et al.*, 2008) have been found. Interestingly, as reported in several other rodent models of the psychotic 'positive-like' symptoms of schizophrenia (see Seeman *et al.*, 2006), an increased proportion of striatal D_2^{High} receptors has been documented in isolation-reared rats (King *et al.*, 2009), which may contribute to dopamine supersensitivity.

Consistent with considerable evidence of hyperactive mesolimbic dopamine activity, a recent *in vivo* electrophysiology study has confirmed an increased number of spontaneously active neurones with a more irregular bursting firing pattern in the VTA of isolation-reared compared to group-housed rats (Fabricius *et al.*, 2010b). Isolation rearing also induces a hyper-responsiveness in dopamine release in the PFc in response to systemic administration of the atypical antipsychotics clozapine and olanzapine, but not haloperidol

(Heidbreder *et al*., 2001). Isolation-reared rats show increased D-amphetamine- and cocaine-induced dopamine release in the nAcc and striatum compared to group-housed controls measured by *in vivo* microdialysis (Jones *et al*., 1992; Hall *et al*., 1998b; Howes *et al*., 2000; Lapiz *et al*., 2003), and enhanced basal and stimulated dopamine and 5-HT release in the nAcc when exposed to conditioned and contextual cues in a conditioned emotional response paradigm (Fulford and Marsden, 1998a; 2007). Collectively, these findings show that the extensive neurochemical imbalances occur in a number of key cortico-limbic brain regions in isolation-reared rats consistent with the validity and usefulness of this paradigm to investigate the aberrant neurobiology underlying schizophrenia.

Much less work has focused on change in glutamatergic receptor density in isolates, and findings are inconsistent. Both down- and up-regulation of PFc NMDA receptor NR2A mRNA expression and no change in PFc, striatal or hippocampal NR1A, NR2B, NR2C, NR2D, NR3A or NR3B subunit expression have all been reported in isolates (Hall *et al*., 2002; Turnock-Jones *et al*., 2009; Toua *et al*., 2010). Although Turnock-Jones reported no change in NR2B subunit protein, down-regulation of the NR2B gene has been reported in the PFc, coupled with increases in NR2A, NR2B, PSD-95 and SAP-102 genes in the hippocampus of isolation-reared rats (Zhao *et al*., 2009). Increased PFc metabotropic mGlurR6 and ionotropic AMPA3 receptor subunit gene expression (Levine *et al*., 2007), and reduced mGluR1 and mGlur5 expression (Melendez *et al*., 2004) are consistent with the proposal that dysregulation of glutamatergic activity may contribute to the behavioural/cognitive deficits associated with social isolation. Indeed, hippocampal synaptophysin (a putative marker of presynaptic glutamatergic activity) is also decreased in isolates (Varty *et al*., 1999). Although alteration in ionotropic and metabotropic glutamate receptor expression has been reported in schizophrenic patients (Meador-Woodruff and Healy, 2000), changes are not all consistent with the rodent findings. Changes in glutamate release and turnover in isolation-reared rats are relatively unexplored. While attenuated PFc glutamate release following injection of mGluR1 and mGluR2 agonists has been reported (Melendez *et al*., 2004), Heidbreder *et al*. (2001) found basal levels of many amino acids (glutamate, glutamine, glycine, GABA, aspartate, alanine, arginine, tyrosine, threonine, taurine and histidine) in the medial PFc to be unaltered by isolation rearing. Furthermore, olanzapine and haloperidol had no effect on any amino acid levels, except glycine, arginine and threonine, while clozapine selectively increased glutamate, alanine and histidine in isolates (Heidbreder *et al*., 2001). Collectively, these findings show that isolation rearing of rat pups from weaning produces subtle, selective and translationally relevant neurobiological alterations in both gene and protein targets, in regions centrally implicated in schizophrenia.

Given the large array of neurochemical and structural changes that have been characterized in the isolation-reared rat, incredibly few studies have attempted to reverse any of these changes with long-term antipsychotic medication. In theory, neurodevelopmental models of schizophrenia offer the ability to perform behavioural, electrophysiological and neurochemical investigations without confounding drug effects, and have potential to detect reversal by agents operating on diverse pharmacological mechanisms. A major weakness of isolation rearing is the relative fragility of behavioural effects that can be reversed by repeated handling or exposure to too many other tests during the developmental period (Weiss *et al*., 1999) and which do not universally occur in every cohort (Cilia *et al*., 2005b; Fone and Porkess, 2008), and the long duration and associated cost of the experiments. However, unlike many other models, post-weaning social isolation is a pure environmental model that requires no physical intervention to either mother or pup, and is relatively simple to execute. This model can also be easily combined with other interventions that could potentially expand the robustness and utility of the paradigm.

Other developmental models

While MAM and isolation rearing have been extensively used as animal models, several other early-life interventions cause neurodevelopmental alterations. For instance, maternal exposure to either bacterial or viral infection during pregnancy elevates circulatory pro-inflammatory cytokines and other mediators of inflammation, affects brain development in the offspring and is associated with an increased risk of schizophrenia (Brown and Derkits, 2010; Brown, 2011). Based on this observation, many groups have attempted to replicate this process in the rodent, via maternal immune activation during a critical mid-gestation window (GD15-19; which approximates to human late third trimester), by the systemic administration of bacterial or viral (-like) agents, and then monitoring the offspring for schizophrenia-like pathologies (for reviews, see Meyer *et al*., 2009; Meyer and Feldon, 2010). The Boksa group compared the effect of prenatal challenge with a variety of immune-activating agents on the development of altered PPI in the offspring, and showed that maternal infection during GD15-19 produced effects dependent on the agent used (Fortier *et al*., 2007; Boksa, 2010; see also Meyer *et al*., 2006a). For instance, an early study showed that exposure of pregnant rats to the bacterial endotoxin, lipopolysaccharide (LPS), increased tyrosine hydroxylase in the nAcc, enhanced amphetamine-induced locomotion (Fortier *et al*., 2004) and impaired PPI, and the authors suggested this might model aspects of schizophrenia (Borrell *et al*., 2002), especially as the deficits in PPI and altered cytokine serum levels were reversed by haloperidol (Romero *et al*., 2007). Furthermore, rats exposed post-natally to LPS (500 $\mu g \cdot kg^{-1}$ i.p. PND 7 and 9) were less active and had impaired object recognition on PND 70 (but not PND 35), and reduced hippocampal (but not PFc) parvalbumin-immunoreactive neurones in the CA1-CA3 (Jenkins *et al*., 2010). Interestingly, other studies found 100 $\mu g \cdot kg^{-1}$ i.p. LPS on GD15–16 reduced the number of ultrasonic vocalizations at PND 3 and 5, impaired nest-seeking behaviour and odour-stroke associative learning at PND 8 and 9, suggesting it reduced social/communicative behaviour in offspring that may relate to childhood and pre-morbid abnormalities reported in schizophrenic subjects (Baharnoori *et al*., 2010). Such early changes may offer the possibility of using neurodevelopmental models of schizophrenia to develop prophylactic rather than curative drug strategies.

Other studies found prenatal immune activation by systemic administration of a by-product of viral replication, polyriboinosinic–polyribocytidilic acid (poly I : C, 4 $mg \cdot kg^{-1}$

on GD15) to pregnant dams causes acute cytokine elevation and, in resultant offspring, the developmental appearance of sensitization to the locomotor effects of both amphetamine (Zuckerman *et al.*, 2003) and the NMDA receptor antagonist, MK-801, and increased time to reach the platform specifically in the reversal learning component of both a T-maze and water maze paradigm (Zuckerman and Weiner, 2005). Similar studies with poly I : C administration to pregnant mice showed that this produced deficits in PPI (Shi *et al.*, 2003), and enhanced methamphetamine-induced locomotion and reduced novel object discrimination, the latter being reversed by 14 days pretreatment with clozapine, but not haloperidol (Ozawa *et al.*, 2006), leading Meyer's group to propose this as a model of schizophrenia (Meyer *et al.*, 2005). Many negative symptoms of schizophrenia, such as alogia, affective flattening and apathy, are virtually impossible to model in laboratory animals (Ellenbroek and Cools, 2000). Offspring from maternal immune-activated mouse dams also show reduced social interaction and anhedonic behaviour (apparent reduced ability to experience pleasure) in a sucrose preference test (thought to resemble the human negative 'symptom-like' domain), together with reduced PFc and hippocampal DA and glutamate levels (Bitanihirwe *et al.*, 2010b). Interestingly, maternal poly I : C administration appears to selectively alter non-spatial information processing, such as novel object recognition, but not novel location learning in the Morris water maze, in resultant offspring (Ito *et al.*, 2010). This poly I : C treatment also disrupts latent inhibition (Zuckerman and Weiner, 2003; Meyer *et al.*, 2006b; Bitanihirwe *et al.*, 2010a) (a behaviour with translational relevance to the pre-attention-processing cognitive domain in humans), which can be restored by acute pretreatment with haloperidol (0.1 $mg \cdot kg^{-1}$) or clozapine (5 $mg \cdot kg^{-1}$) (Zuckerman *et al.*, 2003). In animals, latent inhibition describes the phenomenon where after pre-exposure to a cue having no relevance, they are less able to learn an association of this cue with an aversive unconditioned stimulus (such as a footshock). Patients with acute schizophrenia (and individuals that score high on psychometrically defined schizotypy) have disrupted latent inhibition, which is restored by antipsychotics (see reviews Dunn *et al.*, 1993; Moser *et al.*, 2000), consistent with the animal observations, suggesting strong potential predictive validity of this test. As mentioned previously, an advantage of neurodevelopmental models is the ability to combine this approach with pharmacological and/or genetic manipulations. This is highlighted in a recent study combining maternal immune activation with poly I : C to DISC1 mutant mice (Abazyan *et al.*, 2010), which showed an apparently enhanced 'schizophrenia-related' phenotype compared to either intervention alone, reduced amygdala and periaquaductal grey volume, dendritic spine density and reduced social interaction (Abazyan *et al.*, 2010). Although requiring further characterization before concrete conclusions can be drawn, the increased use of such approaches to neuropsychopharmacological research will only enhance knowledge and reliability of preclinical schizophrenia research.

Finally, simple exposure of pregnant dams to unpredictable stress during the third week of gestation also enhances the locomotor response to amphetamine, impairs PPI and reduces social behaviour (Koenig *et al.*, 2005; Lee *et al.*, 2007) akin to that which would be predicted for a model of schizophrenia. Many similar interventions have been examined, but these have not been extensively characterized, and so are not covered in detail in this review (see Meyer and Feldon, 2010).

Pharmacological models

Amphetamine model of schizophrenia

As dopamine dysregulation with hyperfunction of the mesolimbic dopamine system was the original tenet theory underlying the basis of schizophrenia (Murray *et al.*, 2008), the first animal models were developed on the basis of pharmacological manipulation to attempt to mimic this feature. Amphetamine-induced psychosis was first described in the 1950s with a clinical picture of auditory hallucinations and persecutory delusions resembling positive symptoms of schizophrenia. In rodents, chronic amphetamine administration induces a persistent sensitization, exaggerating the hyperactivity caused by acute amphetamine challenge (Robinson and Becker, 1986; Featherstone *et al.*, 2008), which is thought to more robustly model symptoms than a single injection (Featherstone *et al.*, 2007a). Pre-administration of a low dose of either haloperidol or clozapine prevents the induction of sensitization (Meng *et al.*, 1998). However, Sams-Dodd (1995; 1998) reported that chronic amphetamine did not induce deficits in social interaction in rats (a task thought to map to the social cognition domain, but also used to model negative symptoms of schizophrenia). This failure to induce negative symptoms in animals is in accordance with data in humans (Javitt and Zukin, 1991; although see Srisurapanont *et al.*, 2003). Long-lasting PPI deficits also occur in rats (Tenn *et al.*, 2005; Peleg-Raibstein *et al.*, 2006), although the dosage regimen may influence the deficit (Featherstone *et al.*, 2007a). Amphetamine sensitization may be accompanied by deficits in PFc-dependent cognitive tasks, including deficits in the extra-dimensional shift and reversal learning in the attentional set-shifting task (Fletcher *et al.*, 2005; Featherstone *et al.*, 2008), an increase in omissions in the five-choice serial reaction time task and reduced accuracy with shorter stimulus duration (Fletcher *et al.*, 2007). Furthermore, clozapine, and to a lesser extent haloperidol, attenuates an amphetamine-induced impairment in attention (Martinez and Sarter, 2008). However, repeated amphetamine administration has no effect on either delayed alternation (Stefani and Moghaddam, 2002) or delayed non-match to position (Featherstone *et al.*, 2008) tasks. Hippocampal-dependent cognition also appears to be spared, as repeated amphetamine has no effect on acquisition or retention of spatial visual learning and memory in the Morris water maze (Russig *et al.*, 2003; Featherstone *et al.*, 2008). Thus, cognitive impairment following chronic amphetamine appears to be restricted to some PFc-dependent tasks while hippocampal function is unaltered.

Repeated amphetamine administration causes a number of neurochemical and structural changes that may account for some of the behavioural changes seen. Locomotor sensitization to a challenge of amphetamine is accompanied by an increase in dopamine efflux from the nAcc and dorsal

striatum (Robinson and Becker, 1986; Featherstone *et al.*, 2007a). Repeated amphetamine increases both the number of dendritic branches and spine density in the nAcc shell and PFc (Robinson and Kolb, 1999). Autoradiography shows that expression of the AMPA receptor subunits, GluR1 and GluR2, is decreased in the nAcc, and GluR1 was transiently increased in the PFc (Lu and Wolf, 1999). Furthermore, increased PFc acetylcholine associated with performance of a sustained attentional task is absent in chronic amphetamine-treated rats following a challenge dose (Sarter *et al.*, 2009).

Overall, chronic amphetamine induces psychotic-like changes, but does not replicate the negative or cognitive symptoms seen in schizophrenia. As the model is based on manipulation of the dopaminergic system, it may primarily respond to drugs that affect this neurotransmitter. However, it should be noted that the hyperlocomotion following amphetamine is sensitive to other classes of drugs, including mGluR2/3 agonists (Kim and Vezina, 2002).

PCP models of schizophrenia

In recent years, increasing evidence supports the idea that dysfunction of the glutamatergic system is a primary pathophysiological change seen in schizophrenia (see Olney and Farber, 1995; Tsai and Coyle, 2002; Coyle *et al.*, 2003; Konradi and Heckers, 2003). Pharmacological evidence for the role of glutamate in schizophrenia centres on findings that blockade of the NMDA receptor by non-competitive antagonists, such as ketamine or PCP, induces delusions and hallucinations in otherwise healthy subjects, symptoms commonly seen in schizophrenia (Cohen *et al.*, 1962; Krystal *et al.*, 1994). Furthermore, in both stabilized chronic and acute schizophrenic patients, PCP rekindles and exacerbates positive symptoms (Javitt and Zukin, 1991), and even at low doses, it produces psychotic symptoms in normal volunteers accompanied by progressive withdrawal and poverty of speech, akin to the negative symptoms of schizophrenia (Luby *et al.*, 1959). Additionally, both acute low-dose and chronic recreational use of PCP impair cognitive performance, which is reversed with cessation of drug administration (Cosgrove and Newell, 1991; Javitt and Zukin, 1991).

As PCP induces several symptoms in humans akin to those seen in schizophrenia, it has been used to attempt to produce a pharmacological rodent model of schizophrenia. Acute PCP administration causes hyperlocomotion (Kalinichev *et al.*, 2007), social withdrawal (Sams-Dodd, 1995), and impairment of both PPI (Mansbach and Geyer, 1989) and cognition (Egerton *et al.*, 2005) in rodents. While it is not possible to perform controlled chronic PCP studies in humans, it has been reported that recreational abuse of PCP produces symptoms that persist beyond the end of treatment (Rainey and Crowder, 1975). Additionally, early PET scans suggested that PCP abuse was accompanied by deficits in the temporal and frontal lobes, which parallels changes seen in schizophrenic patients (Hertzmann *et al.*, 1990). Thus, it has been suggested that chronic PCP use may be used to more accurately mimic the symptoms of schizophrenia (Jentsch and Roth, 1999). This has been the basis for evaluating of the effects of chronic PCP administration in rodents; most commonly using twice-daily administration for 7 days followed by a 7 day washout period before the start of experimentation herein described as subchronic. However, different research groups have developed their own variant of the subchronic PCP treatment, detailed analysis of which is beyond the scope of this review, but some distinguishing features are discussed in Table 2. Notably, variations in the period of administration, dose, gender and strain all affect the peak concentration of PCP in the brain, which could account for many differences reported with these various protocols (Table 2).

As with the neurodevelopmental models, hyperlocomotion is frequently used as an index thought to have translational relevance to positive symptoms. Chronic PCP regimes (including 4–10 days, either repeated or intermittent) do not cause spontaneous hyperactivity, but result in locomotor sensitization to a subsequent challenge dose of PCP (Scalzo and Holson, 1992; Xu and Domino, 1994; Johnson *et al.*, 1998; Hanania *et al.*, 1999; Abekawa *et al.*, 2002; Clark *et al.*, 2002; Fletcher *et al.*, 2005; Tenn *et al.*, 2005; McLean *et al.*, 2009). This mirrors the clinic where 'positive symptoms' in normal patients are seen while PCP is on-board (Luby *et al.*, 1959). Sensitization to PCP is attenuated by both typical and atypical antipsychotics, such as haloperidol and clozapine, respectively (Phillips *et al.*, 2001), providing predictive validity to the modelling of positive symptoms. Unlike amphetamine, PCP induces changes reminiscent of not only positive, but also negative symptoms seen in patients with schizophrenia (Jentsch and Roth, 1999). Similarly in the rat, chronic PCP (3–21 days) reduces social interaction (thought to reflect social withdrawal; a negative symptom) (Sams-Dodd, 1996), which is also reversed by both acute haloperidol and clozapine injection (Sams-Dodd, 1998). Additionally, 14 day chronic PCP reduces social behaviour in both rats (Lee *et al.*, 2005) and mice (Qiao *et al.*, 2001), the deficit in mice being reversed by clozapine, but not haloperidol. In contrast, Jenkins *et al.* (2008) reported no overall decrease in social interaction, but an increase in non-contact behaviour in rats following subchronic PCP. These discrepancies may be due to variations in the dosing regimen or the time after administration that social interaction was recorded. Another negative symptom exhibited by schizophrenic patients is dysfunctional reward processing or anhedonia. Interestingly, a patient with schizophrenia typically shows a normal response to an immediate pleasurable stimuli, but they cannot maintain hedonic value, which results in loss of anticipatory pleasure, sometimes referred to as the 'anhedonia paradox' (Pizzagalli, 2010). In rodents, subchronic PCP fails to cause any significant difference in sucrose intake, commonly used to evaluate change in reward (Jenkins *et al.*, 2010), and thus thought to relate to anhedonia seen in schizophrenia.

Although acute NMDA antagonist injection impairs PPI in rodents (Mansbach and Geyer, 1989), the deficit induced by chronic PCP is not sustained, such that the PPI impairment diminishes within days of PCP cessation (Ehrhardt *et al.*, 1999; Martinez *et al.*, 1999; Schwabe *et al.*, 2005; Tenn *et al.*, 2005; Egerton *et al.*, 2008; Tunstall *et al.*, 2009). This recovery may explain some of the discrepancies in cognition tasks observed following PCP administration in rodents. Chronic PCP usually produces cognitive impairment in both rats and mice, irrespective of strain (Table 2, but note Li *et al.*, 2003; Fletcher *et al.*, 2005; Brigman *et al.*, 2009). Fletcher *et al.* (2005) failed to see an impairment in attentional set-shifting with a 5 week (3 $mg \cdot kg^{-1}$) intermittent dosing regimen that

Table 2

Comparison of the effects of various subchronic PCP administration protocols on cognitive paradigms in rats and mice as indicated

Dose	Species/Strain/Sex	Time of test	Behavioural test	Antipsychotic drug effect	Reference
Subchronic (2 mg·kg^{-1})	Rat/Lister hooded/♀	>7 days	Deficit in reversal learning	Reversed by acute ASN, CLZ, OLZ, SRT, ZPD and repeated ASN, RSP and OLZ; no effect of acute HLP or CPM	(Abdul-Monim *et al.*, 2006; Idris *et al.*, 2010; McLean *et al.*, 2010b)
		7 days	Deficit in novel object recognition	Reversed by acute CLZ, MLP, OLZ, RSP, SRT, but not HLP	(Grayson *et al.*, 2007; Idris *et al.*, 2010; Snigdha *et al.*, 2010)
Subchronic (2 mg·kg^{-1})	Rat/Sprague-Dawley/♂	7 days	Deficit in reversal learning		(Jentsch and Taylor, 2001)
			Deficit in novel object recognition	No effect of concurrent RSP	(McKibben *et al.*, 2010)
Subchronic (4.5 mg·kg^{-1})	Rat/Sprague-Dawley/♂	7 days	Deficit in performance in double Y-maze		(Beninger *et al.*, 2010)
Subchronic (5 mg·kg^{-1})	Rat/Lister hooded/♂	7 days	Deficit in episodic memory	No effect of CLZ	(Le Cozannet *et al.*, 2010)
			Deficit in attentional set shifting	Reversed by acute SRT, but not RSP or HLP	(Rodefer *et al.*, 2005; Broberg *et al.*, 2009; Goetghebeur and Dias, 2009)
	Rat/Wistar/♂	72 h	Deficit in delayed alternation task		(Seillier and Giuffrida, 2009)
	Mice/C57BL/6J/♂	7 days	No deficit in operant behaviour or reversal learning		(Brigman *et al.*, 2009)
Chronic intermittent (2.6 mg·kg^{-1}, 28 days)	Rat/Long-Evans/♂	72 h	Impaired attentional set shifting		(Egerton *et al.*, 2008)
		24 h	Deficit in novel object recognition		(Spano *et al.*, 2010)
3 days per week for 5 weeks (3 mg·kg^{-1})	Rat/Sprague-Dawley/♂	4 weeks	No effect on attentional set shifting		(Fletcher *et al.*, 2005)
Osmotic minipump (15 mg·kg^{-1}·day^{-1}, 14 days)	Rat/Lister hooded/♂	7 days	Impaired attentional set shifting		(Pedersen *et al.*, 2009)
12 days (0.5–4 mg·kg^{-1})	Mice/C57Bl/6J/♂	15 min	Impaired spatial learning at low dose	Reversed by repeated CLZ, but not HLP	(Beraki *et al.*, 2008)
14 days (10 mg·kg^{-1})	Rat/Sprague-Dawley and Long-Evans/♂	48 h	Deficit in spatial delay alternation task (at longer delays)		(Jentsch *et al.*, 1997b) (Marquis *et al.*, 2007)
	Mice/ICR/♂	5 days	Deficit in novel object recognition	Reversed by acute and repeated ARP, but not HLP	(Nagai *et al.*, 2009)
	Mice/C57BL/6J and Rat/Sprague-Dawley/♂	7 days	No deficit in spatial performance		(Li *et al.*, 2003)
10 days (with 2 day break) (10 mg·kg^{-1})	Mice/ICR/♂	14 days	Deficit in novel object recognition	Reversed by repeated QTP	(Tanibuchi *et al.*, 2009)
6 days (1.3 mg·kg^{-1})	Rat/Wistar/♂	30 min	Deficit in spatial learning and memory	Reversed by acute CLZ, SRT and RSP; no effect of HLP	(Didriksen *et al.*, 2007)
5 days (b.i.d. 5 mg·kg^{-1})	Rat/Sprague-Dawley/♂	9 days	No deficit in spatial delay alternation task (short delays)		(Stefani and Moghaddam, 2002)
5 days (2 mg·kg^{-1})	Rat/Wistar/♂	30 min	Deficit in attention, cognitive flexibility and speed of processing	Partially attenuated by chronic CLZ, but not QTP	(Amitai *et al.*, 2007; Amitai and Markou, 2009b)

Time of test indicates duration after the last PCP injection that the task was evaluated. Subchronic: PCP twice daily for 7 days, chronic intermittent: PCP once daily for 5 days followed by three times a week for 3 weeks.

Abbreviations: ARP, aripirazole; ASN, asenapine; CLZ, clozapine; CPM, chlorpromazine; HLP, haloperidol; MLP, melparone; OLZ, olanzapine; QTP, quetiapine; RSP, risperidone; SRT, sertindole; ZPD, ziprasidone. Note: As no current antipsychotic drugs reverse cognitive deficits seen in schizophrenia, the translational relevance of these observations in rodents is currently difficult to evaluate, only in future if cognitive enhancers are developed will the true predictive value of these tasks become apparent.

induced locomotor sensitization (Tenn *et al*., 2005). In contrast, Egerton *et al*. (2008) observed impaired performance in the extra-dimensional shift of the attentional set-shifting task following a similar chronic intermittent PCP regimen. However, Egerton *et al*. began with 5 consecutive days of PCP followed by 3 weeks of intermittent dosing, and commenced behavioural testing 3 rather than 7 days after the last dose. This is consistent with the suggestion that cognitive impairment may not be permanent, following an intermittent treatment protocol. It is also possible that the initial 5 consecutive days of PCP injection is crucial to establishing a cognitive deficit, because Egerton *et al*. showed that 5 days of consecutive dosing alone was sufficient to cause cognitive impairment. It is important for a model to induce changes that are stable over time both because this has face validity to the disease and enables predictive evaluation of drug reversal. In addition, with pharmacological models, a suitable 'drug-free washout' ensures results are the consequence of the chronic regime and not due to the presence of the pharmacological effects. However, it appears that some cognitive tasks (such as the five-choice serial reaction time task) may only be impaired shortly after the end of the dosing regimen with the drug on-board, but in these cases, chronic administration may produce a more robust deficit than a single dose of PCP (Amitai *et al*., 2007). Although schizophrenia affects both males and females, there are notable differences in age of onset and response to antipsychotics, which should be replicated in animal models with good face validity. In rats, gender affects both the pharmacokinetics of PCP (Gartlon *et al*., 2006) and cognitive ability (Sutcliffe *et al*., 2007), but the same subchronic PCP dosage regimen impairs reversal learning and novel object recognition equally in male (Jentsch and Taylor, 2001; McKibben *et al*., 2010) and female (Abdul-Monim *et al*., 2007; Grayson *et al*., 2007) rats. As discussed previously, animal tests of cognition have been evaluated to mirror most of the seven cognitive domains thought to be affected in schizophrenia (Hagan and Jones, 2005) and PCP appears to cause deficits in at least five of these (see Table 2 and Neill *et al*., 2010). Chronic PCP impairs working memory (delayed alternation task) (Jentsch *et al*., 1997b; Marquis *et al*., 2007; Seillier and Giuffrida, 2009), attention/vigilance and speed of processing (five-choice serial reaction time task) (Amitai *et al*., 2007; Amitai and Markou, 2009a), visual learning and memory (object recognition) (Grayson *et al*., 2007; McKibben *et al*., 2010; Spano *et al*., 2010) and reasoning and problem solving (attentional set-shifting, operant reversal learning and maze tasks) (Rodefer *et al*., 2005; Abdul-Monim *et al*., 2006; Didriksen *et al*., 2007; Beraki *et al*., 2008; Egerton *et al*., 2008; Pedersen *et al*., 2009; Idris *et al*., 2010), but to date we are unaware of any studies evaluating social recognition following chronic PCP. Although a few of these tasks are performed shortly after the last dose of PCP, such that the results are the combination of acute PCP after a chronic regimen, the cognitive deficits in others are seen after delays of 7 days and persist for weeks afterwards (Neill *et al*., 2010). The persistence of cognitive deficits may have face validity with the disease, but would seem to differ from humans where cognitive deficits appear to reduce after cessation of long-term recreational PCP use (Fauman and Fauman, 1978; Cosgrove and Newell, 1991).

Acute administration of the typical antipsychotic, haloperidol, is unable to reverse deficits in novel object recognition, reversal learning, attentional set shifting and spatial learning induced by chronic PCP (see Table 2 for references). In contrast, many of the PCP-induced cognitive deficits appear to be reversed by several atypical antipsychotics. However, acute clozapine failed to reverse a subchronic PCP-induced impairment in episodic memory (Le Cozannet *et al*., 2010), and only sertindole, but not risperidone, restored performance in the extra-dimensional shift of the attentional set-shifting task (Goetghebeur and Dias, 2009). Few studies have evaluated the effect of repeated or chronic antipsychotic drug treatment on cognitive impairment in PCP models. Repeated risperidone, commenced after subchronic PCP, reversed the impairment in reversal learning (McLean *et al*., 2010b), but when given concurrently, it failed to attenuate a deficit in novel object recognition (McKibben *et al*., 2010). Chronic quetiapine did not improve performance in the five-choice serial reaction time task (Amitai and Markou, 2009b), whereas chronic clozapine partially attenuated the impairment (Amitai *et al*., 2007). In mice, both repeated quetiapine and aripiprazole restored performance in the novel object recognition task (Nagai *et al*., 2009; Tanibuchi *et al*., 2009).

The reversal of PCP-induced cognitive impairments produced by atypical antipsychotics is in marked contrast with clinical evidence, suggesting that these drugs have a relatively small, if any, beneficial cognitive effect and little difference in effectiveness compared with typical antipsychotic drugs (Keefe *et al*., 2007). This raises questions about the predictive validity of the PCP models and the ability to screen out false positives. A recent study has shown that co-administration of the selective 5-HT_{2A} receptor inverse agonists, primavanserin and volinanserin, with ineffective doses of atypical antipsychotics, reversed the subchronic PCP-induced deficit in novel object recognition (Snigdha *et al*., 2010). While the move to testing adjunct therapy is encouraging, use of atypical antipsychotics may confound these experiments, providing false positives. In this case, their effect alongside typical antipsychotics, such as haloperidol, may have more relevance to the clinical treatment of cognitive deficits.

Chronic PCP induces several neurochemical changes that correlate well with those thought to occur in schizophrenia. For instance, the mesolimbic dopamine system in the rat is hyper-responsive to amphetamine and mild stress following chronic PCP (Jentsch *et al*., 1998). Microdialysis data show that both basal and stress-induced PFc dopamine levels are reduced in rats chronically treated with PCP (Jentsch *et al*., 1997b; 1998), consistent with the suggestion of decreased PFc dopamine in schizophrenia patients (Akil *et al*., 1999). Similarly, chronic PCP (10 $mg \cdot kg^{-1} \cdot day^{-1}$ for 14 days) reduces basal PFc glutamate release in freely moving rats (Fattorini *et al*., 2008) and mice, and increases PFc glutamate–aspartate transporter (GLAST) levels in the latter, consistent with cortical glutamatergic hypofunction (Murai *et al*., 2007). Decreased synaptic spines on frontal cortex neurones (Flores *et al*., 2007; although see Hajszan *et al*., 2006) and a reduced number of cortical and hippocampal parvalbumin-immunoreactive neurones are observed following subchronic PCP (Reynolds *et al*., 2004; Abdul-Monim *et al*., 2007; Jenkins *et al*., 2008; 2010; McKibben *et al*., 2010), mirroring deficits seen in schizophrenia. Interestingly, rats treated chronically with MK-801 show

a similar reduction in the number of parvalbumin-containing neurones in the dentate gyrus and CA1 region of the hippocampus, but no change in the PFc (Braun *et al.*, 2007), which supports the preferential use of PCP in pharmacological models. In the chronic intermittent PCP model, reduced basal glucose utilization indicative of hypometabolism occurs in the PFc, reticular nucleus of the thalamus and auditory cortex (Cochran *et al.*, 2003). Furthermore, there is decreased thalamic and PFc parvalbumin mRNA, which is reversed by chronic clozapine, while haloperidol only reversed the effect in the thalamus (Cochran *et al.*, 2003). Interestingly, clozapine reversed the hypometabolism observed in the auditory cortex, but neither drug reversed it in the PFc. The inability of either clozapine or haloperidol to reverse the PCP-induced prefrontal hypometabolism may reflect the inability to restore cognitive deficits in patients (Cochran *et al.*, 2003). Chronic intermittent PCP reduces *N*-acetylaspartate (NAA) and *N*-acetylaspartylglutamate (NAAG) levels in the temporal cortex, and increases NAAG in the hippocampus, which is thought to reflect neuronal dysfunction and closely resembles post-mortem changes seen in schizophrenia (Reynolds *et al.*, 2005). Reductions in mRNA of the GABA-synthesizing enzymes GAD_{67} and GAD_{65}, and the presynaptic transporter GAT-1 also occur along with increases in $GABA_A$ subunits in the cerebellum, following chronic intermittent PCP, findings also akin to those seen in schizophrenia patients (Bullock *et al.*, 2009). Multiple changes in receptor expression have been reported following chronic PCP including: decreased dopamine D_1 expression in the medial and lateral striatum (without changes in D_2 or D_4 receptors), increased 5-HT_{1A} expression in medial–prefrontal and dorsolateral frontal cortices, and altered GABA expression in the Fc, hippocampus and striatum (Choi *et al.*, 2009; Beninger *et al.*, 2010). Long-term decreases in NMDA receptor binding occur in many areas, including the hippocampus, nAcc, caudate putamen, thalamus and cortex, although this pattern of binding was considerably different from that seen immediately after the cessation of dosing, emphasizing the importance of the washout period (Newell *et al.*, 2007).

One of the advantages of chronic PCP models over others is the ability to translate findings to primates. Again, chronic PCP is thought to be a better model than acute PCP in part due to the absence of impaired motor function and motivation (Jentsch and Roth, 1999). PCP twice a day for 14 days in monkeys induced a deficit in a PFc-dependent object retrieval task, which was reversed by acute clozapine (Jentsch *et al.*, 1997a). Additionally, a reduction in PFc parvalbumin-containing neurones also occurs in primates (Morrow *et al.*, 2007). Over a 7 month period, PCP significantly reduced the frequency and duration of primate social behaviour, mirroring the negative symptoms seen in schizophrenia patients (Mao *et al.*, 2008). Interestingly, the 'negative symptoms' produced following 56 days of osmotic minipump infusion of PCP seen by Linn *et al.* (2007) were attenuated by concurrent glycine administration, a class of treatment that has had some benefits as an adjunctive therapy on cognitive and negative symptoms in clinical trials. Thus, chronic PCP models do appear to have some translational relevance across rodents, non-human primates and humans.

One criticism of chronic PCP models is that the intervention is given to adult rats, which does not have construct validity to the proposed neurodevelopmental origin of schizophrenia. The neonatal PCP model of schizophrenia attempts to address this issue. Typically, rat pups receive 10 $mg \cdot kg^{-1}$ PCP on PND 7, 9 and 11. There is mounting evidence that neonatal PCP administration produces enduring behavioural changes in adulthood (Mouri *et al.*, 2007). Corresponding to chronic PCP, locomotor sensitization to PCP challenge has been reported following neonatal PCP, which is reversed by acute administration of the atypical antipsychotics, olanzapine and risperidone (Wang *et al.*, 2001; Anastasio and Johnson, 2008a; Boctor and Ferguson, 2010). Deficits in PPI have been reported by some groups to be attenuated by acute olanzapine and risperidone (Wang *et al.*, 2001; Takahashi *et al.*, 2006; Anastasio and Johnson, 2008a), but not seen following neonatal PCP in other studies (Rasmussen *et al.*, 2007; Boctor and Ferguson, 2009). It should be noted that when PCP was given only once on PND 7, neither deficits in PPI nor locomotor sensitization were reported, emphasizing the importance of the repeated dosing regimen (Anastasio and Johnson, 2008a).

Enduring cognitive deficits have also been reported in the social recognition task (Depoortere *et al.*, 2005; Harich *et al.*, 2007), performance in the Morris water maze (Sircar, 2003; Andersen and Pouzet, 2004), acquisition of a delayed spatial alternation task (Wiley *et al.*, 2003), disrupted performance in a continuous spatial alternation task (Boctor and Ferguson, 2010) and impaired flexibility in a set-shifting task (Stefani and Moghaddam, 2005) with the latter being reversed by acute sertindole (Broberg *et al.*, 2009). That performance in the Morris water maze was improved by chronic D-serine treatment suggests a hypoglutamatergic state occurs in the neonatal PCP model (Andersen and Pouzet, 2004). In contrast, other groups giving repeated neonatal PCP have found no enduring effect on cognition nor any sensitization to the lomotor activity response. Several independent research groups have also shown long-lasting behavioural changes, including increased spontaneous (Harris *et al.*, 2003) (but see Stefani and Moghaddam, 2005; Kawabe *et al.*, 2007) and methamphetamine-induced (Uehara *et al.*, 2010) locomotion, attentuated PPI (provided sufficient treatment length is used) (Uehara *et al.*, 2009; 2010) and deficits in cognition, such as non-matching to position (Kawabe and Miyamoto, 2008) and radial arm maze (spatial working memory) learning and attentional set shifting (Stefani and Moghaddam, 2005) following neonatal administration of MK-801 (typically 0.13–0.4 $mg \cdot kg^{-1}$ s.c. or i.p., PND 7–10 or 20), which are not seen when the drug is given to adult rats (Kawabe *et al.*, 2007). However, neonatal MK-801 (Kawabe *et al.*, 2007; Uehara *et al.*, 2009; 2010) and PCP (Boctor and Ferguson, 2010) cause a significant decrease in body weight across development, a feature not seen in schizophrenia.

The finding that pro-apoptotic genes are up-regulated and anti-apoptotic genes are down-regulated on PND 12 (Wang *et al.*, 2001; Liu *et al.*, 2010) supports the suggestion that the changes following neonatal NMDA receptor antagonists are the result of neurotoxicity preferentially in the frontal cortex (Wang and Johnson, 2005). This neurotoxicity can be prevented by enhancing NMDA receptor function (Lei *et al.*, 2009). Alterations in glutamate function have been reported following neonatal PCP with increased levels of NMDA NR1, NR2A and NR2B subunits in the Fc (Wang *et al.*, 2001;

Anastasio and Johnson, 2008a,b), and increased NMDA receptors in the Fc and hippocampus (Sircar, 2000). Morphological changes in PCP rats including decreased hippocampal volume and neuronal number, and decreased synaptophysin mRNA all support the suggestion of synaptic dysfunction (Wiseman Harris *et al.*, 2003). Furthermore, neonatal PCP also produces a sustained elevation in hippocampal and entorhinal BDNF in 8-week-old rats (Takahashi *et al.*, 2006) similar to clinical observations in the corticolimbic system of patients with chronic schizophrenia (Takahashi *et al.*, 2000). While most studies have occurred in rats, one notable study in mice observed hyperlocomotion, a deficit in spatial working memory and decreased social interaction, the latter being reversed by clozapine (Nakatani-Pawlak *et al.*, 2009). Additionally, the behaviour was associated with decreases in parvalbumin-immunoreactive neurones in the Fc and hippocampus, similar to those seen in chronic PCP-treated rats and schizophrenic patients.

Lesion models

Neonatal ventral hippocampal lesion

Neonatal lesion (PND 7) of the ventral hippocampus (vHip) of the rat (corresponding to the anterior hippocampus in humans) by local injection of the excitotoxin, ibotenic acid (typically 3–5 μg in 0.3 μL (Lipska *et al.*, 1993; Becker *et al.*, 1999) under anaesthesia with hypothermia), causes behavioural abnormalities that emerge after puberty and compromises the architectural integrity of the developing medial PFc and nAcc, which both receive a dense innervation from the former structure (Tseng *et al.*, 2009). The model was developed by the Lipska–Weinberger group in the early 1990s to attempt to mirror emerging brain imaging evidence for the presence of ventricular enlargement and hippocampal changes seen in first-episode schizophrenic patients (Lipska *et al.*, 1993; 1995; Lipska and Weinberger, 1994). As with other developmental models, the time of performing the lesion is critical, and lesions on or after PND 14 produce less pronounced, but immediate onset changes failing, for instance, to enhance apomorphine-induced stereotypy (Wood *et al.*, 1997). Furthermore, the lesion also needs to be bilateral to produce the full spectrum of changes, such as enhanced self-administration of cocaine (Chambers and Self, 2002). The behavioural changes produced by vHip lesions appear progressively with development; deficits in social interaction (thought to have relevance to negative symptoms in schizophrenia) and increased aggression occur by PND 35 and remain (Sams-Dodd *et al.*, 1997), impairment in spatial learning and working memory also appears around PND 25 (Chambers *et al.*, 1996). However, the full behavioural constellation, including locomotor hyper-responsivity to stress (Lipska *et al.*, 1993); enhanced sensitivity to dopamine agonists, such as apomorphine (Lipska and Weinberger, 1993) or amphetamine (Wan *et al.*, 1996; Beninger *et al.*, 2009), and NMDA receptor antagonists, such as MK-801 (Al-Amin *et al.*, 2000) or PCP (Hori *et al.*, 2000), deficits in PPI (Le Pen *et al.*, 2000) and reward (Lipska *et al.*, 1995); and enhanced sensitivity to drugs of abuse, such as cocaine (as reviewed elsewhere Lipska, 2004; Tseng *et al.*, 2009) are not present until around PND 56.

Antipsychotic drug administration either at adulthood [1 mg·kg^{-1} i.p. haloperidol (Sams-Dodd *et al.*, 1997)] or from adolescence [45 μg·kg^{-1} i.p. risperidone, PND35-56 (Richtand *et al.*, 2006)] prevents the hyper-responsivity to amphetamine produced in vHip rats. Interestingly, the increase in aggression and reduction in total social interaction shown by neonatal vHip lesion rats are independent of sexual maturity (Becker *et al.*, 1999) and are not reversed by clozapine (Sams-Dodd *et al.*, 1997).

Although behavioural studies strongly suggest increased mesolimbic dopamine activity in vHip rats, *in vivo* microdialysis shows that nAcc dopamine levels are unaltered under basal conditions (Wan and Corbett, 1997; Brake *et al.*, 1999), and no enhanced dopamine release occurs in response to stress or amphetamine administration from that seen in control rats (Wan *et al.*, 1996; 1998) despite their elevated locomotor response. However, in vHip lesioned rats, raclopride and SCH23390 prevent amphetamine-induced hyperlocomotion, suggesting that this hyper-responsiveness is probably the consequence of increased postsynaptic sensitivity of the dopamine D_2 receptor (Wan and Corbett, 1997) and not altered presynaptic dopamine release. vHip rats also show enhanced acquisition of sucrose and cocaine self-administration, thus demonstrating enhance reinforcement to reward (Chambers and Self, 2002). However, as schizophrenic patients would be expected to show anhedonia and reduced reward, this does not appear to replicate the human condition.

Adult vHip lesioned rats have reduced mPFc levels of NAA (a marker of neuronal integrity) and GAD_{67} mRNA expression (located in GABAergic neurones) (Lipska *et al.*, 2003), and increased $GABA_A$ receptor expression (Endo *et al.*, 2007), together with a reduction in spine density and dendritic length of pyramidal neurones in both the mPFc and nAcc medium spiny neurones (Flores *et al.*, 2005; Marquis *et al.*, 2008). vHip rats also show reduced potassium-induced glutamate release from *ex vivo* PFc slices (Beninger *et al.*, 2009), consistent with cortical glutamatergic hypofunction. Indeed, pulsed stimulation of the VTA source of dopaminergic innervation to the PFc caused enhanced pyramidal neuronal firing in neonatal vHip lesioned rats that was not observed when the lesion was applied to adult rats (O'Donnell *et al.*, 2002). Taken together, this is consistent with vHip causing a developmental alteration in PFc neuronal integrity, which may contribute to the behavioural alterations seen.

vHip lesions in rats cause persistent and marked impairment in several spatial working memory tasks including impaired acquisition of the T-maze delayed alternation (Lipska *et al.*, 2002; Marquis *et al.*, 2006) and Morris water maze (Le Pen *et al.*, 2000; Beninger *et al.*, 2009) tasks, radial arm maze choice accuracy (Chambers *et al.*, 1996) and retention of passive avoidance learning (Le Pen *et al.*, 2000), even with prolonged learning. Recently, it has been shown that vHip rats are impaired in a spatial delayed win-shift radial arm maze task, which is dependent on communication between hippocampus and PFc, but unimpaired in a non-delayed random foraging radial arm maze task requiring connections between the hippocampus and nAcc (Brady *et al.*, 2010), suggesting that disruption of the former pathway may be the primary mediator of spatial working deficits. vHip

lesioned rats also show selective impairment in the extra-dimension phase shift and the following reversal in the attentional set-shift paradigm (Marquis *et al.*, 2008) consistent with behavioural rigidity and impaired attention, and visual processing that may reflect medial PFc dysfunction in this model. Chronic administration of clozapine (2.5 mg·kg^{-1}·day^{-1} i.p.) did not reverse, but exacerbated the radial arm maze choice accuracy deficit in male vHip lesioned rats (Levin and Christopher, 2006), so further pharmacological evaluation is required to determine the predictive utility of this model.

Interestingly, combining social isolation from weaning with vHip lesions further enhances the reduction in dendritic length and spine density of both PFc and Acc neurones seen with either intervention alone (Alquicer *et al.*, 2008; Marquis *et al.*, 2008) and causes an increase in dopamine content of the PFc, which is not seen with vHip lesion alone (Alquicer *et al.*, 2004). Similarly, repeated administration of PCP at adulthood (7.5 mg·kg^{-1} i.p. daily from PND42–55) to neonatal vHip lesioned rats elevated striatal D_1 receptor levels not seen with the lesion and enhanced the hyperactivity response from that of the lesion alone (Hori *et al.*, 2000), consistent with the idea that dual neurodevelopmental and subsequent pharmacological stress may precipitate long-term psychiatric changes akin to those seen in schizophrenia.

Few manuscripts document the success rate, but overall mortality with the vHip lesion appears to be approximately 15% (Richtand *et al.*, 2006), and in some studies as many as 30–33% of treated animals may have unilateral hippocampal damage, which fails to reach histological criteria (Chambers and Self, 2002; Beninger *et al.*, 2009).

In a modification of this neurodevelopmental lesion approach, it has been shown that acute injection of the $GABA_A$ antagonist, picrotoxin into (Bast *et al.*, 2001), or stimulation of the NMDA receptor in (Peleg-Raibstein *et al.*, 2005) the vHip of the adult rat can produce locomotor hyperactivity, attenuation of PPI and enhanced PFc dopamine release analogous to that thought to occur in schizophrenia. However, the short-lasting nature of these effects, and the need to have indwelling cannulae, make these models best suited to examine the neurobiological role of enhanced hippocampal–cortical activity in pyschosis-related behaviour rather than as a tool to evaluate drug reversal.

Genetic models

Knock-out mice

Twin studies unequivocally demonstrate that schizophrenia is predominantly a genetic disorder with heritability estimated to be around 80%; however, no single genetic alteration is causal or sufficient to explain this complex heterogeneous disorder. A large array of candidate genes have been associated with an increased risk of schizophrenia (see reviews by Harrison and Weinberger, 2005; Gogos and Gerber, 2006; Allen *et al.*, 2008b). Meta-analyses of genome-wide studies have identified several linkage regions containing some of the putative susceptibility genes. Furthermore, most disrupted genes predominantly segregate to proteins involved in neuronal plasticity, glutamatergic or dopaminergic function and synaptogenesis (Harrison and Weinberger, 2005). Multiple susceptibility genes acting synergistically and in conjunction with epigenetic processes and early-life environmental adverse effects are thought to contribute to the risk of developing schizophrenia. However, there may be multiple very rare genetic mutations that are highly penetrant that may contribute to the illness (Walsh *et al.*, 2008).

The majority of genetic models have been developed on the basis of replicating changes in mRNA and protein seen in schizophrenia. Furthermore, particular emphasis has been placed on developing models of individual schizophrenia endophenotypes, which have been proposed to be present stable, measurable, intermediate disease features that bridge the gap between the overt manifestations of schizophrenia and underlying risk genes (Gottesman and Gould, 2003; Braff *et al.*, 2007; O'Tuathaigh and Waddington, 2010).

The progress made from genetic models of schizophrenia has recently been extensively reviewed by Waddington and colleagues (Arguello and Gogos, 2010; van den Buuse, 2010; Jaaro-Peled *et al.*, 2010; O'Tuathaigh and Waddington, 2010; O'Tuathaigh *et al.*, 2010). The vast array of genetic models produced is beyond the scope of this review, but a selection of models which have contributed significantly to the understanding of aberrant role of dopamine and glutamate function in the pathophysiology of schizophrenia, are discussed herein.

DISC1

One of the earliest genes implicated in the development of schizophrenia was *disrupted-in-schizophrenia 1* (*DISC1*). DISC1 is a synaptic protein expressed early in development playing a crucial role in pre- and post-natal neurone development, which is particularly active during synaptogenesis, neuronal migration and synaptic plasticity (Jaaro-Peled, 2009). Although the link between a mutated *DISC1* gene and increased susceptibility for schizophrenia is contentious, studies have found positive linkage (Millar *et al.*, 2001). Development of a knock-out mouse has proven challenging; however, seven different strains of transgenic mice containing inducible and/or partial *DISC1* gene mutations resulting in a (partial) loss of DISC-1 function have been created and used to investigate schizophrenia (see Jaaro-Peled, 2009 for review).

Several pathological and behavioural alterations in DISC-1 mice resemble symptoms of schizophrenia. DISC-1 transgenic mice have enlarged lateral ventricles, and reduced cortical thickness and brain volume (Jaaro-Peled *et al.*, 2010). Some, but not all, DISC-1 mutants show reduced parvalbumin immunoreactivity in the mPFC and hippocampus – two regions centrally implicated in the cognitive dysfunction associated with psychosis (Clapcote *et al.*, 2007; Hikida *et al.*, 2007; Shen *et al.*, 2008; Jaaro-Peled *et al.*, 2010). Furthermore, reductions in hippocampal dendritic complexity, structure and density occur in some DISC-1 mutants, consistent with a genetic link to cognitive impairment seen in schizophrenia (Li *et al.*, 2007b; Kvajo *et al.*, 2008). Behaviourally, subtle deficits in PPI reported in some DISC-1 transgenic mice are reversed by both haloperidol and clozapine (Clapcote *et al.*, 2007; Hikida *et al.*, 2007), which is in keeping with clinical findings, but not in other studies (Pletnikov *et al.*, 2008). Similar discrepancies occur in open field/spontaneous

locomotor activity paradigms, where some DISC-1 transgenics show locomotor hyperactivity (Clapcote *et al.*, 2007; Hikida *et al.*, 2007), while others do not (Koike *et al.*, 2006; Li *et al.*, 2007b; Pletnikov *et al.*, 2008). As an index of negative symptoms, there are conflicting reports of the impact on social interaction with some studies showing reduced sociability in DISC-1 mutants (Clapcote *et al.*, 2007; Li *et al.*, 2007b; Desbonnet *et al.*, 2009), whereas others report no difference (Hikida *et al.*, 2007). Some deficits in working memory and executive function have been reported in some DISC-1 mutant mice (Pletnikov *et al.*, 2008), while performance in the Morris water maze task, novel object recognition and fear-conditioning tasks were essentially normal (Hikida *et al.*, 2007; Kvajo *et al.*, 2008; Arguello and Gogos, 2010). Some of these discrepancies may relate to the method of production of the transgenic animal rather than DISC-1 changes *per se*. No studies to date have examined whether these cognitive changes can be reversed by existing antipsychotic drugs or novel pro-cognitive agents.

Neuregulin1 and ErbB4

Another leading candidate 'risk' gene is *neuregulin-1 (NRG1)* and its receptor *ERBB4* (Harrison and Law, 2006a; Mei and Xiong, 2008). The *NRG1* gene gives rise to a number of different proteins (I–VI) with diverse isoforms (31 in total) of neuregulin, all having distinct expression patterns and functions (Mei and Xiong, 2008). NRG1 is a pleiotropic growth factor containing an epidermal growth factor (EGF)-like domain critically involved in the development and functioning of the nervous system. As well as being involved in both excitatory and inhibitory neurotransmission in the mature brain, NRG1 is also involved in synaptogenesis, neuronal migration, myelination, neurone–glial interactions and glial cell formation in the developing brain (Harrison and Law, 2006a; Mei and Xiong, 2008; van den Buuse *et al.*, 2009). NRG1 interacts with tyrosine kinase receptors, of which ErbB4 is its predominant partner. Distinct patterns and levels of expression of NRG1 isoforms are present in all tissues (Mei and Xiong, 2008).

Homozygous knock-out of NRG1 is developmentally lethal in mice; however, viable heterozygous, hypomorphic/conditional knock-outs that can modulate neuregulin–ErbB4 signalling have been developed, all with distinct 'schizophrenia-like' alterations (Harrison and Law, 2006a; Mei and Xiong, 2008). For example, mice with heterozygous deletion of the EGF-like domain [Nrg1(ΔEGF)$^{+/-}$], heterozygous deletion of the transmembrane domain of NRG1 [Nrg1(ΔTM)$^{+/-}$], deletions of the immunoglobulin (Ig) domain [Nrg1(ΔIg)$^{+/-}$] and homozygous deletions of NRG1-cleaving enzyme BACE [Nrg1(BACE)$^{-/-}$] all show distinct, varied schizophrenia-related alterations in behaviour and pathophysiology (Mei and Xiong, 2008; Jaaro-Peled *et al.*, 2010). The post-mortem findings associating NRG1 changes with schizophrenia are varied; however, studies have reported increased expression of both NRG1 and NRG4 in the PFc and hippocampus (Hahn *et al.*, 2006; Harrison and Law, 2006b; Law *et al.*, 2006). To this end, two heterozygous, hypermorphic transgenic mouse strains have been recently described, which express GFP-tagged type-1 NRG1 cDNA (Kato *et al.*, 2010). In addition, a homozygous deletion of the primary receptor of NRG1, ErbB4, has also been developed (Erbb4$^{-/-}$).

Nrg1(ΔTM)$^{+/-}$ mice are hyperactive in an open-field and in an alternating Y-maze task, an effect reversed by clozapine. They also show subtle impairments in PPI of acoustic startle (Stefansson *et al.*, 2002; O'Tuathaigh *et al.*, 2007; van den Buuse *et al.*, 2009). However, upon administration of psychostimulants, such as amphetamine, these mice are no longer hyperactive and do not show impaired PPI compared to wild type (Stefansson *et al.*, 2002; van den Buuse *et al.*, 2009). These mice also show increased aggression, impaired social novelty, but normal social interaction compared to wild-type controls and normal working memory in a spontaneous alteration task (O'Tuathaigh *et al.*, 2007; 2010). Some of these traits, including increased spontaneous locomotion and impaired PPI, are replicated in the Nrg1(ΔEGF)$^{+/-}$ mouse (Stefansson *et al.*, 2002), but no difference in the mutant and wild-type mouse response to psychostimulants occurred in either task (Duffy *et al.*, 2008). Nrg1(ΔEGF)$^{+/-}$ mice show robust deficits in social interaction, and are cognitively impaired in contextual fear conditioning and mismatched negativity, but not novel object recognition tasks (Ehrlichman *et al.*, 2009; Arguello and Gogos, 2010; O'Tuathaigh *et al.*, 2010). In contrast, Nrg1(ΔIg)$^{+/-}$ mice are not spontaneously hyperactive and show normal working memory in a spontaneous alteration task, but have impaired latent inhibition (Rimer *et al.*, 2005). Proteolytic processing of NRG1 has profound effects on the behavioural phenotype. Nrg1(BACE)$^{-/-}$ mice show both spontaneous and psychostimulant-induced locomotor hyperactivity, impaired PPI and reduced responses to social novelty compared to wild-type mice (Savonenko *et al.*, 2008; van den Buuse, 2010), the first two of which are reversed by clozapine (Savonenko *et al.*, 2008). Interestingly, the hypermorphic strains over-expressing GFP-tagged type-1 NRG1 cDNA showed considerable overlap with traits seen in the hypomorphic models, including increased spontaneous locomotor activity, reduced PPI, impaired contextual fear conditioning and reduced social interaction (Kato *et al.*, 2010). Conversely, these mice have increased parvalbumin-positive neurones in the PFc and reduced, rather than the expected elevated, hippocampal and PFc levels of dopamine and tyrosine hydroxylase activity (Kato *et al.*, 2010). In relation to ErbB4, homozygous knock-out mice have subtle elevations in locomotor activity, but no change in PPI compared to wild type (Stefansson *et al.*, 2002; Golub *et al.*, 2004), but show significantly reduced social interaction (Roy *et al.*, 2007). Although these genetic models are interesting tools to study 'schizophrenia-like' phenotypes, it should be noted that their construct validity, with the possible exception of the NRG1-type 1 cDNA strains, is questionable because the clinical manifestation of schizophrenia is associated with NRG1 hyper- rather than hypo-function (Hahn *et al.*, 2006; Harrison and Law, 2006b; Law *et al.*, 2006). In addition, the diversity and lack of consistency of effects in hypomorphic models, and the similarity in effects between hyper- and hypomorphic models, together with the lack of pharmacological studies, means that much more work is required before the functional relevance of NRG1 changes can be evaluated.

In addition, the diversity and lack of consistency of effects, together with a lack of pharmacological studies, mean that much more work is required before the functional relevance of NRG1 changes can be evaluated from a drug discovery perspective.

Dysbindin

One of the many potential molecular targets thought to underlie alterations in neurotransmitter release seen in schizophrenia is dysbindin. Dysbindin is a synaptic protein thought to regulate exocytosis, vesicle biogenesis and receptor trafficking involved in excitatory synaptic neurotransmission (Karlsgodt *et al.*, 2011; Papaleo *et al.*, 2010). The protein is encoded by the gene dystobrevin-binding protein 1 (*DTNBP1*) currently thought to be one of the most promising candidate genes for schizophrenia susceptibility, mutations of which show strong correlations with schizophrenia susceptibility and onset in patients (Williams *et al.*, 2005; Allen *et al.*, 2008a; van den Buuse *et al.*, 2009). Reduced expression of dysbindin in the dorsolateral PFc and hippocampus occurs in post-mortem tissue from patients with schizophrenia, and reduced protein expression has been linked to negative symptoms (Weickert *et al.*, 2004; 2008; Papaleo *et al.*, 2010).

A naturally occurring mutant [known as the 'sandy' (*sdy*)] mouse has a homozygous, spontaneous deletion in exon 2 of the *DTNBP1* gene, resulting in complete loss of dysbindin protein expression (Papaleo *et al.*, 2010). A back-cross of the spontaneous dysbindin mutant onto the C57BL/6J strain causes homo- and hetero-zygous mutants (Papaleo *et al.*, 2010), showing a number of pathological hallmarks relevant to schizophrenia. Such mutants display alterations in dendritic spines of excitatory asymmetric synapses in the hippocampal CA1 region with narrower synaptic clefts in excitatory junctions, broader postsynaptic densities and a reduced number of larger presynaptic glutamatergic vesicles (Chen *et al.*, 2008; Feng *et al.*, 2008; Jaaro-Peled *et al.*, 2010). The phenotype of $Dys^{-/-}$ and/or $Dys^{+/-}$ mice has yet to be thoroughly characterized, but recent studies show them to be hyperactive in the open field (Cox *et al.*, 2009; van den Buuse, 2010; Papaleo *et al.*, 2010) and hyper-responsive to amphetamine-induced locomotion (Papaleo *et al.*, 2010). Interestingly, $Dys^{-/-}$ mice showed increased basal startle and PPI responses inconsistent with other mutant mice (Papaleo *et al.*, 2010). Furthermore, these effects were reversed by the dopamine D_2 receptor agonist, quinpirole, but not the antagonist, eticlopride (Papaleo *et al.*, 2010). Altered working memory, including increased acquisition of a spatial T-maze paradigm, and impaired performance during a discrete paired-trial task under more demanding conditions (further enhanced by mild stress) occur in $Dys^{-/-}$ mice (Papaleo *et al.*, 2010). Reduced social contact in a dyadic social interaction test (Feng *et al.*, 2008; O'Tuathaigh *et al.*, 2010), impaired spatial reference memory and novel object recognition, but enhanced contextual fear conditioning, have also been reported in dysbindin mutants (Feng *et al.*, 2008; Takao *et al.*, 2008; Bhardwaj *et al.*, 2009; Arguello and Gogos, 2010).

Reelin

As previously discussed, reelin is implicated in synaptic formation and plasticity within the CNS (Cassidy *et al.*, 2010a), and reelin mRNA and protein are significantly reduced in the cerebellum, hippocampus and Fc of patients with schizophrenia. The homozygous 'reeler' knock-out mouse has gross behavioural abnormalities, including aberrant gait, far more extreme than behavioural changes seen in schizophrenia (Bellon *et al.*, 2009). In contrast, a spontaneous mutation – a deletion of one allele encoding the reeler gene – results in a viable heterozygous mutant mouse (O'Tuathaigh *et al.*, 2010). As well as showing schizophrenia-related pathology including increased neuronal packing and reduced dendritic spine density in the frontal cortex and hippocampus (Liu *et al.*, 2001; Krueger *et al.*, 2006), reeler mice have a behavioural phenotype with some relevance to symptoms seen in schizophrenia.

Reeler mice show increased social dominance potentially akin to negative-like symptoms, but demonstrate normal social interaction (Podhorna and Didriksen, 2004; Tueting *et al.*, 2006). However, modulation of reelin expression in wild-type mice via promoter hypermethylation does reduce social interaction in a novel environment (Tremolizzo *et al.*, 2005). Given that reductions in reelin expression occur in areas implicated in cognition, such as the hippocampus and PFc, it is surprising that reeler mice show relatively few prefrontal-related cognitive deficits (Krueger *et al.*, 2006; Arguello and Gogos, 2010). Some inconsistencies in retention of conditioned fear (Qiu *et al.*, 2006) (associative learning) have been reported, but reeler mice showed normal behavioural flexibility in a reversal learning and inhibitory control task (Krueger *et al.*, 2006), normal acquisition and retention of spatial reference memory in the Morris water maze (Krueger *et al.*, 2006; Arguello and Gogos, 2010), normal performance in a three-choice serial reaction time task and normal working memory in a delayed matched to position task (Krueger *et al.*, 2006). At most, reeler mice show subtle deficits in acquisition of reversal learning and inhibitory control tasks (Krueger *et al.*, 2006; Arguello and Gogos, 2010), so they fail to replicate the cognitive impairment seen in schizophrenia. The reports of 'positive-like' phenotype symptoms in the reeler mouse are also inconsistent. For example, the heterozygous reeler mouse shows an enhanced locomotor response to the psychostimulant, methamphetamine (Matsuzaki *et al.*, 2007; van den Buuse, 2010); however, spontaneous locomotion is reduced in this mutant and interestingly only the spontaneous hypoactivity is reversed by olanzapine (Ognibene *et al.*, 2008). Mixed effects on PPI have also been reported, altered PPI and basal startle responses occurring in homozygous, but not heterozygous mutant mice (Salinger *et al.*, 2003), while others have reported an age-dependent impairment in heterozygous reeler mice, that is, highly sensitive to environmental stress (Tueting *et al.*, 2006). Furthermore, disrupted PPI in reeler mice appears highly dependent on the type and duration of the testing protocol used (Barr *et al.*, 2008; van den Buuse, 2010). Additional studies have shown the heterozygous reeler mouse to be less sensitive to early maternal separation than wild type (Ognibene *et al.*, 2008), suggesting that this mutation may confer resistance to phenotypic changes driven by early-life adversity. Thus, data suggest that although the reelin protein may be implicated in disrupted processes centrally involved in schizophrenia, it appears that the use of reeler mice as a potential genetic model to improve our understanding of the neurobiological basis of schizophrenia requires further validation.

Apomorphine susceptibility and apomorphine unsusceptibility rats

The dopamine D_1/D_2 receptor agonist, apomorphine, induces several typical dopamine-mediated behaviours, such as locomotor hyperactivity; climbing behaviour; and stereotype

grooming, licking and gnawing. Selective breeding of Wistar rats, which show a heightened stereotype behavioural response to systemic administration of apomorphine, was used to develop the apomorphine susceptible (APO-SUS) rat line, and behaviour compared with those showing a diminished response, the apomorphine unsusceptible (APO-UNSUS) rat (Cools *et al.*, 1990; Ellenbroek and Cools, 2002). These two strains showed 'mirror image' responses in terms of behaviour, neurobiology and immune responses (Cools *et al.*, 1990; 1993a,b; Ellenbroek and Cools, 2002). This approach highlights how valuable spontaneous genetic variation in strains and breeding lines can be manipulated to research the contribution that interactions between gene and environmental stressors can make to disease (van Loo and Martens, 2007). Similar to that expected in schizophrenic patients, APO-SUS rats show impaired PPI and latent inhibition in a conditioned taste aversion paradigm, enhanced responses to novelty in an open field and to psychostimulants, and increased aggression towards a resident intruder (Cools *et al.*, 1990; Ellenbroek and Cools, 2002). The enhanced response to novelty in the APO-SUS rat is accompanied by potentiation in amplitude and time of nAcc dopamine release compared to the APO-UNSUS rats (van Elst *et al.*, 2005). Such animals have a higher level of tyrosine hydroxylase in the striatum indicative of increased dopamine synthesis and increased dopamine D_2 receptor levels in the nAcc (van der Elst *et al.*, 2005) (although similar changes seen in post-mortem tissue from patients with schizophrenia may be secondary to antipsychotic medication). Interestingly, further supporting the construct validity of APO-SUS rats as a model of schizophrenia, their pups have a somewhat retarded somatic development compared with APO-UNSUS rats, which also compares to findings in pre-schizophrenic infants (Degen *et al.*, 2005). Few, if any, studies have reported the predictive validity of the APO-SUS/APO-UNSUS rats, and thus further work is required before judgement can be made on the utility of this animal model in the drug discovery process. However, the insight provided by a model utilizing natural gene and environmental stressor interactions could be invaluable in understanding disease pathology.

From the models reviewed above, it is apparent that creating and/or characterizing rodents with genetic mutations in several molecular targets thought to be relevant to schizophrenia is a worthwhile strategy to improve understanding of the neurobiological contribution that each gene product may have to phenotypic alterations seen in schizophrenia. Given the rich pharmacology of antipsychotic therapies currently tested in these models, it is difficult to assess their true predictive validity, and as with other animal models of schizophrenia, there is some way to go before they are fully validated and can be used as tools with any predictive validity to help develop novel therapeutic compounds acting against current drug resistant features of the disorder. Given the inability of current antipsychotics to treat all symptoms of the disorder, and the as-yet limited availability of true cognitive enhancers, treatment strategies may shift so that 'prevention rather than cure' approaches may be adopted. In which case, the information gleaned from genetic animal models would greatly assist targeting selective susceptibility genes. Individual genetic mutations may confer susceptibility by converging to alter a common pathophysiological process, but this is only likely to be identified if multiple genetic alterations are induced simultaneously, but will go undetected in simple genetic knock-out animals. Given the complex nature of gene–gene and gene–environment interactions, using models where a single gene with a potential link to schizophrenia has been permanently altered is unlikely to represent the true complex nature of the disorder. To address these issues, more complex models, with altered genetic approaches (such as inducible and tissue-specific knock-outs) are currently in development, which will go some way to addressing some of the confounds associated with compensatory mechanisms and will help expand the potential use of genetic models in schizophrenia research. By adopting a more conditional approach, modulating selected genes in a temporal and/or tissue-specific manor, the effect of compensatory mechanisms may be reduced and the relevance of genetic manipulation to schizophrenia enhanced. As mentioned previously, another potential beneficial future development would be to focus on combining mutations and integrating such transgenic animals with pre-existing environmental or pharmacological models of the disease to attempt to produce more embracing models of the disorder.

Conclusion

In schizophrenia, the poor patient response to current antipsychotics may largely be due to the focus on reversal of the symptoms rather than addressing prevention of development of the underlying causal structural alterations that could be evaluated in neurodevelopmental models. Similarly, one of the greatest impediments to the development of new therapeutics is the lack of understanding of the mechanisms underlying disease pathology in schizophrenia, resulting in a lack of molecular targets. A major reason for the high attrition of potential new antipsychotics in the clinic is the unreliable predictive power of animal models of schizophrenia, which tend to overestimate actual clinical efficacy. Focus on the ability of acute, rather than chronic, drug administration to reverse changes seen in animal models may have contributed to their unreliability, but the development of new behavioural tests with greater translational relevance to the negative and cognitive symptoms is also essential. No single animal model will be able to mirror all the complex sequelae manifest of such a complex and heterogeneous disorder. However, as highlighted in this review, most of the proposed rodent models of schizophrenia replicate changes in mesolimbic dopamine function, which may contribute to the positive symptoms seen in schizophrenia. In contrast, far fewer, such as MAM, neonatal vHip lesion, isolation rearing from weaning and chronic PCP, also cause changes reminiscent of negative and cognitive impairments probably as a consequence of alterations in frontal cortical–limbic circuits. A major advantage of neurodevelopmental over pharmacological or lesion models of schizophrenia is the ability to perform behavioural, electrophysiological and neurochemical investigations in the absence of confounding drug or surgical interventions, and the potential to be able to detect reversal by agents operating on multiple pharmacological mechanisms that are vital to identify new classes of antipsychotic agents and pro-cognitive compounds to be used as

adjunct therapeutics. In contrast, neurodevelopmental changes and compensatory mechanisms brought into play by constitutive knock-out of genes may limit the utility of genetic models of schizophrenia. Furthermore, given the heterogeneity of changes observed in schizophrenia, animal models based on manipulation of a single gene have not surprisingly struggled to replicate the full syndrome of this complex disorder. Instead, the approach is intended to delineate the relationship between individual genes and the underlying pathophysiology and specific endophenotypes of the disorder. Genetic models have also contributed to understanding some causal disease factors and may help identify potential biomarkers of therapeutic relevance. Despite this, there is no evidence that any genetic model is used in the drug discovery process or in routine use to screen potential new antipsychotic agents.

The use of animal models to improve understanding of the neurochemical and structural CNS changes that precipitate development of schizophrenia, rather than a focus on treating the symptoms, is a prerequisite to enable new more effective therapeutic strategies to be developed. The complex and unclear nature of gene–gene and gene–environment interactions in the aetiology of schizophrenia means that the challenge to develop more reliable predictive animal models of this disorder, probably through using multiple early-life intervention, is still ongoing.

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Conflict of interest

The only conflict to declare is the source of funding; there are no others.

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