Advancing schizophrenia drug discovery: optimizing rodent models to bridge the translational gap

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Abstract | Although our knowledge of the pathophysiology of schizophrenia has increased, treatments for this devastating illness remain inadequate. Here, we critically assess rodent models and behavioural end points used in schizophrenia drug discovery and discuss why these have not led to improved treatments. We provide a perspective on how new models, based on recent advances in the understanding of the genetics and neural circuitry underlying schizophrenia, can bridge the translational gap and lead to the development of more effective drugs. We conclude that previous serendipitous approaches should be replaced with rational strategies for drug discovery in integrated preclinical and clinical programmes. Validation of drug targets in disease-based models that are integrated with translationally relevant end point assessments will reduce the current attrition rate in schizophrenia drug discovery and ultimately lead to therapies that tackle the disease process.

Schizophrenia is a severely debilitating form of mental illness that affects 1% of the global population. Patients exhibit symptoms that include hallucinations and delusions (known as positive symptoms), avolition and reduced affect (known as negative symptoms) as well as cognitive deficits (BOX 1). The diversity of these clinical symptoms, and the fact that they overlap with symptoms present in other forms of mental illness such as bipolar disorder, raises questions about the future classification and diagnosis of neuropsychiatric disorders in general. Research suggests that schizophrenia results from a combination of genetic, neurodevelopmental and environmental risk factors[1,2]. However, our ability to diagnose schizophrenia — based on biomarkers that reflect causal genetic, biochemical and pathophysiological events — is in its infancy. Schizophrenia is usually diagnosed in late adolescence or early adulthood, and patients require medication throughout their lives. Existing medications — which primarily target dopamine receptors — do not cure the disease, fail to alleviate many of the symptoms of the disorder and have many serious side effects. Hence, new improved therapies are urgently required. Understanding the complex neurobiology underlying the 'troubled mind' in schizophrenia is key to the development of new treatments.

Antipsychotic drugs have been the mainstay of schizophrenia treatment for several decades. The introduction of chlorpromazine in the 1950s revolutionized the treatment of the disorder; however, it was not until the 1970s that advances were made in the understanding that the binding affinity of antipsychotic drugs to the dopamine D2 receptor subtype correlated with their clinical efficacy in alleviating hallucinations and delusions. At the neuronal level, these drugs are thought to block dopamine receptors in the mesolimbic dopaminergic system to alleviate the psychotic (positive) symptoms. An unfortunate consequence of this is that dopamine blockade in the nigrostriatal and hypothalamic–pituitary systems results in unwanted side effects resembling Parkinson's disease (known as extrapyramidal side effects) and hyperprolactinaemia, respectively.

This profile, along with other side effects such as sedation and hypotension, led to the development of other therapeutic strategies, including the development of agents targeting specific dopamine receptor subtypes or a range of receptors (known as multi-affinity receptor target agents), as well as the development of compounds with a balance of activity against 5-hydroxytryptamine (5-HT; also known as serotonin) receptors versus D2 receptors, with the hope of obtaining an improved therapeutic profile. The term 'atypical drugs' (also known as second-generation drugs) was introduced to suggest that these newer compounds were a substantial improvement

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doi:10.1038/nrd3649
Published online 22 June 2012

Box 1 | **Symptoms of schizophrenia**

Schizophrenia was first described by Kraepelin and Bleuler at the turn of the twentieth century. It is typically classified into three broad clusters of symptoms that can be further subdivided into various domains and subdomains (or constructs). There is an evolving debate on which domains and/or subdomains are core to the disease, although the neurobiological mechanisms that underpin them are not completely understood.

Positive symptoms. Positive symptoms consist of hallucinations (typically auditory) and delusions, and are amenable to drug therapy.

Negative symptoms. Negative symptoms encompass blunted affect, deficits in social functioning, anhedonia, avolition and poverty of speech. Avolition and diminished emotional expression are key negative symptom subdomains, whereas poverty of speech and inappropriate affect are more related to cognitive symptoms[119]. Avolition (lack of motivation) rather than anhedonia is likely to be a core symptom of the disorder as patients can experience pleasure even though their outward expression of emotions is reduced. Patients have a reduced capacity to anticipate whether the pursuit or achievement of a goal will be pleasurable. These symptoms are resistant to treatment.

Cognitive deficits. Cognitive deficits are arguably the most debilitating and enduring deficits in schizophrenia and remain resistant to treatment. Cognitive impairments occur in a range of neuropsychological tests; they are present in patients who have never been medicated and they are observed before the onset of psychosis, suggesting that they are core deficits of the illness[120]. Around 20–60% of the variance in functional recovery is explained by cognitive performance. Thus the potential to enhance functional outcome has been a major driver for developing novel treatments, and has led to the establishment of major initiatives to tackle this problem, such as the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) initiative and the CNTRICS (Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia) initiative. Cognitive symptoms include deficits in working memory, executive control, attention, long-term memory, perception and social cognition. Each of these cognitive domains can be subdivided into distinct subdomains (also known as constructs).

over the 'typical' older drugs, such as chlorpromazine and haloperidol, in terms of treating a broader range of symptoms and reducing their side-effect profile. Over time, the appropriate use of the term 'atypical' has become blurred; perhaps a clearer definition of drug 'atypicality' is that the drug has a similar efficacy to typical drugs but fewer extrapyramidal side effects.

The various hypotheses concerning the mechanism of action of these drugs, from a receptor pharmacology perspective, are summarized in TABLE 1 and BOX 2 (also reviewed in REF. 3). Despite the abundance of proposed receptor-mediated mechanisms to explain drug atypicality, all existing antipsychotic drugs target dopamine receptors to varying degrees. This commonality in mechanism of action underpins the dopamine hypothesis of schizophrenia. A considerable body of evidence supports the notion that the positive symptoms of schizophrenia are related, at least in part, to aberrant mesolimbic dopamine transmission, and can thus be ameliorated via antipsychotic drugs that block dopamine receptors[4–6].

Although it has been postulated that atypical drugs can treat all the symptoms of schizophrenia with fewer extrapyramidal side effects (because they have reduced effects on the nigrostriatal pathway compared to typical drugs), this notion has recently been challenged. The CATIE (Clinical Antipsychotic Trials in Intervention Effectiveness) studies[7] demonstrated similar efficacy and extrapyramidal side-effect profiles for both typical and atypical drugs but there were some confounding issues related to dose selection.

In essence, drug treatment for schizophrenia has not advanced substantially in the past 50 years. Nevertheless, advances have been made in understanding the potential role of other receptors (in addition to dopamine receptors) in contributing to drug efficacy, as well as the involvement of these receptors in specific side effects[8,9]. However, the view that all antipsychotic drugs need to produce a degree of D2 receptor blockade to be clinically effective against psychotic symptoms remains a contentious topic.

Atypical antipsychotic drugs have a limited ability to improve cognitive deficits or negative symptoms. As these symptoms are the strongest predictors of long-term functional outcome for patients[10], they represent a large unmet therapeutic need. So where do we go next? Given that D2 receptor blockade does not ameliorate the negative symptoms and cognitive deficits associated with schizophrenia, much of the current opinion regarding which preclinical disease models could be useful for predicting clinical drug efficacy is erroneous.

The development of new preclinical models for cognitive deficits and negative symptoms is a major challenge as it relies on an understanding of the neurobiological processes that underpin these clinical symptoms and the ability to translate these into an equivalent animal model. Characterization of cognitive dysfunction in psychiatric diseases is therefore paramount to inform animal models[11]. Various initiatives and consortia have been set up to tackle this unmet clinical need (BOX 3). Specific consortia aim to ascertain which specific subsets of symptoms (or domains) are most amenable to modelling in a preclinical context. These consortia include the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) and CNTRICS (Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia) initiatives.

Other consortia are adopting multipronged approaches for the discovery of new medicines (for example, NEWMEDS (Novel Methods Leading to New Medications in Depression and Schizophrenia), which is funded by the Innovative Medicines Initiative; see the NEWMEDS website) or they are evaluating the potential clinical efficacy of new compounds (for example, TURNS (Treatment Units for Research on Neurocognition and Schizophrenia); see the TURNS website). Crucially, these consortia evaluate the robustness of laboratory tests and the reproducibility of results across sites.

Strategies for drug discovery: keys to success

Two essential factors for developing new strategies for improved drug discovery in schizophrenia. First, the disease model should be based on known pathophysiological, genetic and environmental risk factors — that is, it should have demonstrable construct validity. Second, the assays for the phenotypic assessment of the model should be translational. For example, the neurobiology underpinning the behaviour of interest should overlap in rodents and in humans. Clearly there are huge challenges

Avolition
Generalized lack of motivation to perform tasks or undertake activities: probably linked to other negative symptoms such as social withdrawal and anhedonia (inability to take pleasure in activities).

Reduced affect
Loss of emotional responsiveness (for example, when talking); characteristic of schizophrenia and major depressive disorder.

Construct validity
An animal model has construct validity when the experimental mechanisms used to create the model are related to the underlying mechanisms involved in disease aetiology.

Table 1 | **Receptor and side-effect profiles of a selection of antipsychotic drugs**

Drug	Receptor affinity								Side effects			
	D1	D2	α1-AR	H_1	mAChR (M1–M4)	5-HT_{2A}	5-HT_6	5-HT_7	EPS	Sedation	Hypotension	Other
Typical antipsychotics												
Haloperidol	++	++++	++	–	–	++	–	+	***	~	**	Minimal anti-cholinergic side effects
Chlorpromazine	++	+++	+++	++	++	++/+++	+++	++	**	**	**	Anticholinergic side effects (dry mouth, constipation, blurred vision)
Thioridazine	++	++/+++	+++	–	++/+++	++	+++	++	*	**	**	Anticholinergic side effects (dry mouth, constipation, blurred vision)
Atypical antipsychotics												
Clozapine	++	+	+++	+++	++/+++	+++	+++	+++	~	**	*	Agranulocytosis (1%); regular blood counts required; salivation (M3-mediated?); weight gain
Olanzapine	++	+++	+++	+++	++/+++	+++	+++	++	*	**	*	Weight gain (5-HT_{2C} mediated?)
Risperidone	++	+++	+++	+	–	++++	+	+++	*	**	*	Weight gain
Quetiapine	++	++	+++	++++	–	++	–	–	~	**	*	Weight gain
Aripiprazole	+	++++	++	++	–	+++	+	+++	~	*	*	Minimal weight gain

–, minimal affinity (>1 μM); +, low affinity (101–1,000 nM); ++, moderate affinity (11–100 nM); +++, high affinity (1–10 nM); ++++, very high affinity (<1 nM); ~, minimal side-effect profile; *, mild side-effect profile; **, moderate side-effect profile; ***, severe side-effect profile; α1-AR, α1-adrenergic receptor; 5-HT_{2A}, 5-hydroxytryptamine receptor 2A; D1, dopamine D1 receptor; EPS, extrapyramidal side effects; H_1, histamine receptor H_1; mAChR (M1–M4), muscarinic acetylcholine receptor subtypes M1–M4.

in modelling complex disorders such as schizophrenia, in which many components of the disease are uniquely observed in humans. Nevertheless, it is important to emphasize that a single model can have utility without fully recapitulating the disease.

By assessing compounds in translational assays using models with construct validity, the selection of potential clinically efficacious compounds in Phase I trials will be enhanced and the rate of attrition will be reduced as compounds progress along the drug discovery pipeline. Close integration of preclinical and clinical teams, along with appropriate consideration of key issues such as pharmacokinetic variables, is essential for these translational neuroscience strategies to be successful.

Below, we provide an overview of current and emerging pathophysiological and genetic models in the context of the assays used for drug discovery that putatively assay positive, negative and cognitive symptoms (for a critique of the assays, see BOXES 3,4).

Models based on the glutamate hypothesis

The glutamate hypothesis of schizophrenia has developed from the observation that administration of NMDA (*N*-methyl-D-aspartate) receptor antagonists — such as phencyclidine (PCP) and ketamine — induces a psychosis in humans that closely resemble schizophrenia, encompassing the negative and positive symptoms of the disease as well as the cognitive deficits[12,13]. Furthermore, these drugs exacerbate symptoms in patients with schizophrenia. Mechanistically, it is thought that acute NMDA receptor blockade leads to symptoms of schizophrenia by blocking tonically active NMDA receptors on GABA (γ-aminobutyric acid)-ergic interneurons, which in turn leads to the disinhibition of pyramidal cell firing. The resulting increase in glutamate release, particularly in the prefrontal cortex, is postulated to be linked to the behavioural deficits observed[14,15].

The relationship between the disruptive effects of acute ketamine administration on cognition in healthy volunteers and in patients with schizophrenia remains unclear. The picture is further confounded by the recent findings that ketamine appears to have antidepressant activity, potentially via modification of the mammalian target of rapamycin (mTOR) pathway[16]. However, genetic and molecular analyses of post-mortem brain tissues also indicate that a dysfunctional glutamatergic system is implicated in schizophrenia. Robust observations include reduced expression of presynaptic proteins, such as vesicular glutamate transporter 1 (VGLUT1; also known as SLC17A7) together with synaptophysin, synaptotagmin and synaptosomal-associated protein 25 kDa (SNAP25)[17–19], along with altered postsynaptic glutamate receptor expression in both the prefrontal cortex and the hippocampus[20].

Pyramidal cell
A large neuron with a cell body roughly in the shape of a pyramid. These neurons use glutamate as their transmitter, and in many cases send fibres for considerably long distances to stimulate neurons in other parts of the brain.

Box 2 | **Treatments for schizophrenia**

Existing treatments for schizophrenia were developed using preclinical models based on the dopamine hypothesis. The dopamine hypothesis of schizophrenia originated in the 1960s from the observations that psychostimulant drugs (for example, amphetamine), which enhance neuronal dopamine levels, can lead to psychotic symptoms that are almost indistinguishable from schizophrenia. The concept that antipsychotic drugs act by blocking dopamine D2 receptors has been put into the context of symptom alleviation by Kapur[6]. It is advocated that the normal role of dopamine in the mesolimbic pathway is to mediate the 'salience' of environmental events and internal representations. In schizophrenia the proposed hyperdopaminergic state may lead to a distortion of how the patient assigns relevance to a particular experience. It is posited that hallucinations may reflect the actual experience of attributing abnormal salience to internal representations, whereas delusions may be a cognitive effort by the patient to make sense of these abnormal experiences.

Antagonism of specific dopamine receptors

It has been argued that D2 receptor blockade could explain the clinical efficacy of both typical and atypical antipsychotic drugs[121]. However, this does not explain the fact that clozapine can improve positive symptoms at a lower D2 receptor occupancy (30–60%) than other drugs. D2 receptor blockade does not improve negative symptoms or cognitive deficits, as evidenced by the limited efficacy of existing drugs. D1 receptor antagonism in the prefrontal cortex may be important, particularly in the actions of clozapine. However, other receptors or combinations of receptors may also be key. Sulpiride and amisulpride are relatively selective for D2 and D3 receptors, with minimal affinity for α-adrenergic receptors, muscarinic acetylcholine receptors and 5-hydroxytryptamine (5-HT; also known as serotonin) receptor subtypes. Neither sulpiride nor amisulpride has an improved therapeutic profile over drugs that have a broader receptor profile. Other studies have suggested that D2 receptor occupancy and/or off rate may be an important determinant of drug efficacy (reviewed in REFS 122,123).

Partial D2 receptor agonists

Aripiprazole, one of the more recently introduced atypical drugs, is considered to be a partial agonist of the D2 receptor. On this basis, it is posited to enhance dopamine activity in areas of the brain where there is a low dopaminergic tone, and inhibit activity where there is a high dopaminergic tone. With regard to schizophrenia, one hypothesis is that aripiprazole reduces the activity of the hyperactive mesolimbic dopaminergic neurons that mediate psychosis while simultaneously enhancing the activity of underactive mesocortical dopamine neurons that are proposed to be involved in the cognitive and negative symptoms of the disorder. Aripiprazole also acts as an antagonist of 5-HT_2 receptors and a partial agonist of 5HT_{1A} receptors[124].

Serotonin–dopamine ratio

The serotonin–dopamine antagonism theory proposed by Meltzer[125] argues that drug 'atypicality' is conferred by a higher affinity of a drug for 5-HT_{2A} receptors relative to dopamine D2 receptors. Risperidone is an example of a drug that falls into this class (TABLE 1).

Multiple-affinity receptor target agents

Many atypical drugs have affinity for multiple receptors, including D1 receptors, D2 receptors, α1-adrenergic receptors, muscarinic receptors and various 5-HT receptor subtypes (TABLE 1). These drugs include clozapine, olanzapine, risperidone and quetiapine. However, these drugs bind differentially to these receptors. For example, olanzapine has a high affinity for most of these receptors, risperidone has a particularly high affinity for 5-HT_{2A} receptors, and quetiapine has a higher affinity for α-adrenergic receptors than for dopamine receptors[123]. Interestingly, many atypical drugs have affinity for 5-HT_6 receptors; the hallucinogenic drug lysergic acid diethylamide (LSD) also binds to these receptors. However, it should be noted that many typical drugs also act on several receptors, and so the hypothesis that atypicality is based on multiple receptor targets does not hold.

Genetic association and copy number variation studies are, at the very least, consistent with a causal role for glutamate synapse disruption in disease aetiology[21,22]. Thus there is compelling converging pathophysiological and molecular evidence supporting the 'glutamate hypofunction' hypothesis of schizophrenia. To this end, NMDA receptor antagonists are widely used in preclinical research for modelling aspects of schizophrenia.

Over the past decade, many academic and commercial groups have exploited NMDA receptor antagonist models in drug discovery (reviewed in REFS 23,24); below, we provide a synopsis of these studies, with emphasis on the translational capacity of the models and the impact that this has had on drug discovery.

It is important to highlight that NMDA receptor antagonists have been used in numerous acute- and repeated-dosing regimens in drug discovery. Furthermore, some behavioural measures are taken in the presence of NMDA receptor antagonists, whereas others are taken following cessation of NMDA receptor treatment (which may have been administered in a vulnerable neurodevelopmental period or during adulthood). Not surprisingly, a plethora of data has emerged that has not produced a consistent picture or even provided clear predictive evidence for compounds that have antipsychotic activity. Superimposed on this is the fact that numerous behavioural phenotypes have been measured, several of which have a limited relationship to schizophrenia. The developmental timing and nature of aberrant glutamate transmission is likely to be fundamental to this chronic disorder. Arguably, models that involve chronic NMDA receptor antagonist administration are most likely to correspond to the disease state, whereas acute models are most likely to represent acute psychotic states.

Compound evaluation in assays of potential relevance to positive symptoms. Many studies involving the acute dosing of NMDA receptor antagonists have used

behavioural assays that were previously used for identifying dopamine antagonists when the dopamine hypothesis of schizophrenia prevailed. This derivative approach confirmed that 'typical' antipsychotic drugs such as haloperidol could reverse acute NMDA receptor antagonist-induced increases in locomotor activity and deficits in prepulse inhibition (PPI).

Following the characterization of a broader range of drugs, it became apparent that compounds such as clozapine, quetiapine and olanzapine were more effective at blocking PCP-induced PPI deficits than haloperidol. This, along with the reduced propensity of these drugs to induce catalepsy in rodents, led to the suggestion that these second-generation drugs were 'atypical' and may be clinically advantageous over 'typical' drugs. The introduction of several of these compounds (risperidone, olanzapine, quetiapine and ziprasidone) in the 1990s and early 2000s led to a wave of enthusiasm about their potential clinical advantages over the older typical drugs. Unfortunately, this enthusiasm has now been dispelled by the results of the CATIE studies[7]. Interestingly, the ability of antipsychotic drugs to restore PPI deficits in patients is not validated to the same extent as in preclinical studies. Furthermore, some NMDA receptor antagonists such as ketamine do not appear to produce PPI deficits in humans[25], raising the possibility that these symptoms are not related to positive or cognitive symptom domains.

How have the aforementioned preclinical studies helped in drug discovery? In general, reversal of deficits in PPI and locomotor activity (induced by the acute dosing of NMDA receptor antagonists) has shown some predictive validity in the identification of antipsychotic drugs. However, it is unclear whether the rescue of these behaviours by putative antipsychotic drugs in acute NMDA receptor antagonist models offers any advantage — namely, in the identification of compounds that have superior efficacy to typical drugs — over the rescue of these behaviours in traditional dopamine-related models.

Compound evaluation in assays of putative relevance to negative symptoms. Antipsychotic drugs have been shown to restore PCP-induced deficits in social behaviour[26]. As current antipsychotic drugs are not clinically efficacious against negative symptoms, this assay does not show good predictive validity.

Compound evaluation in assays of relevance to cognitive domains. The development of new drugs has been hampered by the lack (or minimal efficacy) of existing drugs for treating the cognitive deficits associated with schizophrenia; there is no gold-standard positive-control drug that can be used in cognitive assays.

Other limiting factors include drug dosing regimens, the use of behavioural assessments that cannot be translated (or can only be partially translated) into the clinic as well as the insensitivity of some of the instrumentation that is used to measure cognitive symptoms in patients with schizophrenia.

The ability of several atypical antipsychotic drugs to restore NMDA receptor antagonist-induced deficits in cognitive behavioural tasks, including novel object recognition, is in line with the limited translational relevance of these assays and the false positives that are often generated[27].

Cognitive behavioural tasks that show promise in a drug discovery context include the 5-choice serial reaction time task (5-CSRTT) and the attentional set-shifting task (ASST) (BOX 3). In the 5-CSRTT, clozapine has a limited ability to restore subchronic and chronic NMDA receptor antagonist-induced deficits in performance[28], paralleling its limited efficacy in the clinic. Studies involving the acute dosing of NMDA receptor antagonists are confounded by the effects of both PCP and clozapine on locomotor activity, further emphasizing the importance of subchronic and chronic NMDA receptor antagonist models in drug discovery[28,29]. Nicotine and nicotinic acetylcholine receptor α7 (α7 nAChR) agonists are effective at improving cognitive performance in the 5-CSRTT task. The limitation of many studies using these translationally relevant end point measures is that these measures have generally not been applied to a disease model with construct validity. It is important to emphasize that the use of a translationally relevant assay in combination with a relevant disease model will provide the greatest chance of success for drug discovery.

Compounds that act at the α7 nAChR have modest cognition-enhancing effects in cognitive tasks in naive (untreated) animals[30], but their translation into the clinic is proving to be equivocal; although a proof-of-concept Phase I clinical trial of the α7 nAChR partial agonist DMXB-A (3-2,4 dimethoxybenzylidene) in patients with schizophrenia found that the drug improved neuropsychological measures, a subsequent Phase II trial found no associated changes in cognition[31,32].

Another drug of considerable interest is modafinil. Originally used as a wake-promoting agent for the treatment of narcolepsy, emerging evidence from small-scale clinical trials shows that modafinil can improve cognitive deficits in patients with schizophrenia[33,34]. Specifically, modafinil reverses intradimensional–extradimensional deficits in the CANTAB (Cambridge Neuropsychological Test Automated Battery) test in patients. In parallel, modafinil restores subchronic PCP-induced deficits in the extradimensional–intradimensional shift in the rodent ASST[35,36]. Importantly, existing antipsychotic drugs have limited effects in this model. Together, these findings suggest that the restoration of subchronic PCP-induced deficits in the ASST may have good predictive validity for assessing cognition-enhancing agents in schizophrenia.

Novel compounds such as phosphodiesterase inhibitors and 5-HT_6 receptor antagonists are also reported to have efficacy against PCP-induced extradimensional–intradimensional deficits[37,38], thus providing proof of principle that phosphodiesterases and the 5-HT_6 receptor are possible therapeutic targets. It should be emphasized however, that the ASST is preclinically very labour intensive. In addition, in some experiments that use the ASST, drugs have been claimed to be cognition enhancers but there has been no clear difference in the ability of control animals to complete the extradimensional shift relative to the intradimensional shift[27]. This suggests that

Prepulse inhibition
(PPI). A reduction in the magnitude of the startle reflex that occurs when an organism is presented with a non-startling stimulus (a prepulse) before being presented with the startling stimulus. Deficits in PPI have been observed in patients with schizophrenia as well as in patients with other psychiatric and neurological disorders.

Predictive validity
An animal model has predictive validity when predictions (for example, of drug efficacy) made using the model are informative for when an equivalent drug is used clinically in patients.

Attentional set-shifting task
A task that is used for assessing rule learning and cognitive flexibility in rodents. Animals learn a set of stimulus–reward associations (for example, a particular odour associated with food reward) while simultaneously ignoring another stimulus (for example, texture). The rules are then changed such that texture is the salient stimulus.

Intradimensional–extradimensional shift
A test of rule acquisition and reversal that is sensitive to frontostriatal regions.

Box 3 | **Behavioural assays: cognitive deficits**

Translational assays that make use of analogous clinical processes and utilize similar neural circuitry are most likely to predict clinically relevant cognition-enhancing compounds. Moreover, the assay should distinguish between specific cognitive deficits and poor performance resulting from generalized deficits (for example, low motivation or sedation). Such assays, informed by cognitive neuroscience, allow valid translation from animals to humans and vice versa.

Although many preclinical assays are being used in drug discovery, few fit the above criteria; this imperfect construct validity implies that these assays have limited predictive validity. Here, we summarize those assays that more closely fit the cognitive neuroscience-informed CNTRICS (Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia) criteria (see REF. 27 for a detailed discussion on assays based on the broader MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) recommendations).

Attention

Attention can be divided into components such as divided and focused attention. Attentional deficits are present in schizophrenia, although the particular components that are most affected are still under debate. At a CNTRICS meeting, assays that incorporate the control of attention were nominated as having the greatest promise for clinical studies[129].

The 5-choice serial reaction time task (5-CSRTT), sustained attention task and the lateralized reaction time task are well-characterized tasks that are performed in rodents for measuring attention[130]. The 5-CSRTT is of particular interest because of its similarities with the continuous performance task, which is performed in humans. The 5-CSRTT is a visuospatial attention assay in which animals have to divide their attention on a sustained basis (via visual search) in order to detect brief visual target stimuli (lights) presented randomly in one of five locations (apertures) over a large number of trials. The task can also incorporate elements of increased attentional demand as well as inhibitory control (animals have to withhold responses under certain conditions).

The task provides comprehensive measures of attention and inhibitory control (premature responding) together with measures of processing speed, motor effects and cognitive flexibility (for example, perseveration). Assessing a range of cognitive components (constructs) is advantageous in studying potential cognition enhancers as it enables the isolation of specific constructs, as well as possible adverse effects, to be identified in a single test. The tasks in both humans and animals involve the prefrontal cortex and thalamus, although the precise brain circuitry involved is not completely identical between humans and animals. Nevertheless, the 5-CSRTT demonstrates considerable construct validity.

Executive control

Executive control is an umbrella term for an array of higher-order processes. Deficits in executive control can affect performance in other tasks including those that measure attention and working memory. The 'rule learning and selection' elements of executive control can be assessed by the intra- and extradimensional (ID–ED) set-shifting task (which is part of the computerized CANTAB (Cambridge Neuropsychological Test Automated Battery) test)[131].The rodent analogue of the ID–ED task is the attentional set-shifting task (ASST)[132]. In this task, rodents learn a series of discriminations of increasing difficulty, including the ID–ED discrimination. Typically, these discriminations involve associating a particular stimulus (for example, odour) with a food reward while simultaneously ignoring another stimulus (for example, texture).

Based on imaging and lesion studies, the ID–ED task has been associated with the dorsolateral prefrontal cortex in humans and the medial prefrontal cortex in rodents[132]. Hence the ASST shows functional homology with the human task and good construct validity. Although widely used in rat models, various methodological considerations — such as its low throughput — limit its use in drug discovery.

Working memory

Deficits in working memory are well documented in patients with schizophrenia, and it is considered that working memory has some executive control component.

The challenges of developing translational working memory tasks in rodents have been discussed in the literature[133]. One concern is that current animal models measure what is more akin to short-term memory rather than working memory. In addition, in several purported working memory tasks rodents are required to hold a single piece of information with minimal executive demand (for example, a delayed match to sample task). Another important difference is that in humans the prefrontal cortex and parietal cortex are involved in spatial working memory tasks, whereas in animals these tasks are often dependent on the hippocampus[27,134]. The challenge is to develop rodent models that incorporate executive control and the focused recruitment of the prefrontal cortex. One possibility is the adaption of the radial arm maze task or other operant tasks in designs that model working memory tasks in humans, such as the *n*-back task[134].

Other constructs and the MATRICS cognitive test battery

Other constructs highlighted in the CNTRICS criteria include long-term memory, perception and social cognition. Although there is a large amount of published literature describing potential animal models of these behaviours, they do not accurately reflect the processes that occur in humans[133]. Hence, it is challenging to develop translationally relevant animal models of long-term memory, perception and social cognition.

However, numerous cognitive tasks have been developed, including the novel object recognition task and other forms of cognitive flexibility, such as reversal learning. Although these tasks have been widely applied in schizophrenia drug discovery (reviewed in REF. 27), and many studies have shown that currently used antipsychotic drugs reverse deficits in these tasks (in attempts to validate the task in a particular model), the fact that existing antipsychotic drugs have minimal or no efficacy in ameliorating cognitive deficits in the clinic suggests that these tasks are generating false-positive results and will have limited predictive validity[27].

Clinical evaluation

TURNS (Treatment Units for Research on Neurocognition and Schizophrenia) is a network of academic sites in the United States that are evaluating the potential cognition-enhancing efficacy of identified targets in proof-of-concept clinical studies or clinical trials. Initial target selection included α7 nicotinic acetylcholine receptor agonists, dopamine D1 receptor agonists and glutamatergic agents acting at either ionotropic or metabotropic receptors.

Cognitive caveats

Despite recent advances in cognitive neuroscience in relation to schizophrenia, the current understanding of the precise neuropsychological components (or constructs) and the neural circuitry that underpins these components is still evolving. Hence, further adaptations of clinical tests as well as tests in animal models will be necessary to ensure valid translation across species. In addition, in the drive to mirror human and animal constructs of cognition that are relevant to schizophrenia, the following points should be considered:

- Rodents are, in many instances, not equipped with the necessary neuroanatomical machinery to perform certain human cognitive constructs (for example, verbal working memory)
- The behavioural outcome that is reflected by the recruitment of a particular neural system may manifest differently between rodents and humans
- The behavioural test may not measure the same animal and human construct (for example, working memory)
- The neural circuits for a particular construct may vary between animals and humans
- The prefrontal cortex is important in working memory, executive function and attention; hence, approaches other than measuring behaviour are required to investigate these components

Overall, there is an appreciation that currently used behavioural assays of cognition need to be refined if they are to identify processes that are relevant to the cognitive symptoms of schizophrenia and thereby have utility in schizophrenia drug discovery.

Box 4 | **Behavioural assays: positive and negative symptoms**

Positive symptoms

Locomotor activity. The development of current antipsychotic drugs for treating the positive symptoms of schizophrenia has been largely influenced by the use of assays based on the dopamine hypothesis. Locomotor activity testing has been widely used, because such assays have a relatively high throughput, and because the role of dopamine in the control of movement — albeit complex — is well established. The enhanced locomotor response to dopaminergic compounds (for example, amphetamine) is associated with altered mesolimbic dopamine transmission and provides a proxy marker for detecting positive symptoms[64].

Although the behavioural consequences of increased dopaminergic activity are different in humans and mice, there may be shared components of the underlying neurotransmitter mechanisms[64]. A number of caveats exist: locomotor activity is a nonspecific behaviour; the equivalent of locomotor activity in humans is unclear; and compounds could reduce locomotor activity by various mechanisms that may not necessarily be related to antipsychotic activity.

Prepulse inhibition. Prepulse inhibition (PPI) measures sensorimotor gating of the startle reflex and relates to the ability of a non-startling pre-stimulus to inhibit the response to a startling stimulus (for example, an auditory or tactile stimulus). PPI is disrupted in schizophrenia and may relate to pre-attentional filtering, which is a precognitive process that prevents sensory overload and cognitive fragmentation (reviewed in REF. 126). As PPI is a cross-species phenomenon, it offers some face validity as a behavioural assay. Although reversal of PPI deficits induced by amphetamine and/or apomorphine is often used as a predictive assay for antipsychotic activity in preclinical rodent models, the exact relationship between PPI and specific symptoms in schizophrenia remains to be clarified[27]. There are also differences in the responses observed between rats and mice, and even between different strains of mice, in terms of baseline responses and responsiveness to antipsychotic drugs.

In addition to schizophrenia, PPI deficits are observed in various other neuropsychiatric diseases including Huntington's disease, bipolar disorder and obsessive compulsive disorder. Perhaps this is not surprising, given that the neural circuitry that underpins PPI involves diverse neural systems encompassing the brainstem and pedunculopontine as well as hippocampal, amygdaloid and prefrontal cortical regions[63].

In summary, reversal of dopamine-mediated hyperlocomotor activity and PPI deficits offers some predictive validity in the identification of antipsychotic compounds as treatments for the positive symptoms of schizophrenia. In addition, despite their limitations, these assays are used to assess schizophrenia-like behaviours in other models (for example, NMDA (*N*-methyl-D-aspartate) receptor antagonist models and genetic models) for the purposes of drug discovery.

Negative symptoms

The development of assays that reflect the negative symptoms of schizophrenia in rodent models represents a considerable challenge. Clearly, some of these symptoms are uniquely observed in humans and are not readily accessible in animal models. Furthermore, the clinical heterogeneity of negative symptoms and the limited understanding of the underpinning neurobiology confounds the development of translationally relevant assays. Nevertheless, various assays have been developed[127], including measurements of social behaviours, anhedonia, blunted affect (emotional expression) and avolition. Most studies have examined social behaviours but it is currently unclear how these behaviours correspond to human behaviours, and anxiety-induced confounding factors are implicit in these tests. Similarly, reduced emotional expression has been examined in anxiety tests such as the elevated plus maze test, but the extent to which these tests represent anxiety disorders in humans is unsubstantiated.

Anhedonia is typically measured using a sucrose preference test and shows sensitivity to antidepressant drugs. However, given that avolition rather than anhedonia is now considered to be an important feature of the negative symptoms of schizophrenia[119], the sucrose preference test is unlikely to represent a useful assay. The same argument can be applied to other tests that assess behavioural despair (such as the forced swim test and the tail suspension test) and are also sensitive to antidepressant drugs.

Avolition is arguably the component of negative symptoms that is most relevant to the disease, and there is a substantial amount of literature on the neurobiological mechanisms underpinning motivation in preclinical settings[128]. Operant assays that measure motivation include progressive ratio tasks, in which animals work to obtain a food reward. Animals are required to press a lever or poke their nose into an aperture an increasing number of times over successive trials to obtain a food reward. The 'breakpoint' is defined as the first criterion level that the animal is unable to complete, and provides an index of avolition. The translational potential of these tests (which may be considerable) has yet to be fully exploited.

In summary, until there is a better understanding of the neurobiological mechanisms underlying the negative symptoms of schizophrenia, there can be no certainty regarding the predictability of preclinical assays for drug discovery. To date, the assays that hold most promise are the operant-based motivational tasks.

Continuous performance task
A task that measures the ability of a subject to maintain sustained and selective attention and inhibitory control.

Radial arm maze
Usually an eight-armed maze that can be used for various memory tasks. In the context of working memory, a rodent explores the eight arms in search of food. Working memory can be assessed by measuring how often the animal returns to an arm that it has already visited and emptied of food reward.

n-back task
The subject is presented with a series of stimuli and is required to respond when the stimulus on the current trial matches that presented *n* trials ago. The memory load can be increased by increasing *n*. The subject has a dual task: to encode the current stimulus and to compare it with that presented on the *n*-to-last trial.

Sensorimotor gating
A process of filtering redundant or unnecessary stimuli in the brain.

Face validity
An animal model or assay in which the outward signs resemble the human condition but may not necessarily be a result of the same underlying mechanism.

Operant assays
Tasks in which the subject learns to behave in such a way to obtain rewards or avoid punishments.

Parvalbumin
A calcium-binding protein expressed in a subset of GABA (γ-aminobutyric acid)-ergic cells, including cortical and hippocampal basket and chandelier cells as well as reticular thalamic neurons. Levels of parvalbumin in some areas of the cortex and hippocampus are reduced in post-mortem tissue samples taken from patients with schizophrenia.

these animals have failed to adequately acquire key components of the task and so the results from such studies should be interpreted with caution.

The potential of drugs to affect distinct cognitive symptoms (or domains) emphasizes the importance of assessing novel compounds in a range of behavioural assays (as highlighted above). Furthermore, to increase the translational relevance of behavioural assays, it will be necessary to carry out further optimization of existing assays and to develop new behavioural tasks that more closely resemble specific subsets of human cognitive symptoms that are underpinned by similar circuitry.

Models based on the GABA hypothesis

There is a close relationship between GABAergic and glutamatergic neurons in regions of the brain that are involved in schizophrenia. Importantly, the high activity of NMDA receptors on parvalbumin-containing

GABAergic interneurons highlights the fact that blocking NMDA receptor activity will have an impact on GABAergic transmission[39]. This is proposed to be particularly important during the vulnerable developmental period[40]. It is therefore not surprising that key deficits in GABAergic pathology have been demonstrated in schizophrenia. Importantly, parvalbumin-containing GABAergic interneurons are important in the generation of γ-oscillations, which are important in cognition and disrupted in schizophrenia.

Post-mortem studies on central nervous system tissue have revealed that markers of particular subpopulations of GABAergic interneurons — namely parvalbumin-containing basket cells and chandelier cells (axo-axonic cells) — are decreased in the prefrontal cortex and temporal cortex of patients with schizophrenia[41,42]. Parvalbumin is expressed at a relatively late stage during development, and because it contributes to neuroprotection the basket and chandelier cells may be vulnerable to perinatal ischaemic episodes. Hence, a primary role for GABAergic interneuron dysfunction in the aetiology of schizophrenia is in line with the known developmental risk factors of the disease[43,44].

Furthermore, there is mounting genetic and molecular evidence for the altered expression of GABA type A ($GABA_A$) receptor subunits and GABA signalling in schizophrenia[45,46]. Although there is strong evidence that deficits in GABAergic neurons are present in patients with schizophrenia, only specific subpopulations of GABAergic interneurons are likely to be involved, and selectively targeting these pharmacologically is challenging. $GABA_A$ receptor subtypes that are specific to these interneurons have not yet been identified, but a $GABA_A$ α2- and α3-subtype-selective modulator had modest cognition-enhancing effects in a small group of patients with schizophrenia[47]. Based on the robust evidence for cortical GABAergic dysfunction in schizophrenia, preclinical models have focused on modifying GABAergic transmission indirectly (using NMDA receptor antagonists) rather than directly (using drugs that act on GABA receptors). Future strategies for drug discovery could focus on restoring the dysfunction in GABA-mediated disturbances in γ-oscillations, which may underpin the cognitive deficits observed in schizophrenia.

Neurodevelopmental models

Antenatal and perinatal environmental factors substantially increase the risk of developing schizophrenia; of these, prenatal infection or malnutrition and obstetric complications are among the most established risk factors[48]. This knowledge has stimulated the development of models based on direct prenatal and/or perinatal damage to the central nervous system. The rat neonatal ventral hippocampal lesion model is used to study the consequences of early damage to the hippocampus[49]. Although the construct validity of this model is lower than the construct validity of some other models, some neurochemical and behavioural changes are observed that can be linked to schizophrenia[50–52], and PPI deficits are ameliorated by the administration of atypical antipsychotic drugs in this model[52].

In a related approach, rats exposed to the toxin methylazoxymethanol (MAM) *in utero* at embryonic day 17 (E17) exhibit impaired cortical development and a loss of parvalbumin-containing interneurons, in addition to deficits in working memory, set-shifting and PPI in adulthood[53]. There is little information available at present as to how sensitive these MAM-induced changes are to antipsychotic drugs.

Rearing of rats in isolation has also been used to model aspects of schizophrenia, as this affects the development of various regions of the brain (such as the prefrontal cortex) and leads to lasting PPI deficits[54]; however, it is worth remembering that childhood trauma is not a major risk factor for this disease[48]. Maternal administration of the viral mimetic polyinosinic:polycytidylic acid (polyI:C) at E15–E17 reportedly produces a spectrum of neurochemical and behavioural changes in the offspring that can be related to schizophrenia[55]. Some of these changes are sensitive to antipsychotics[56].

Overall, it is likely that the greatest utility of neurodevelopmental models — such as maternal polyI:C administration — may be observed in combination with genetic models, as this would allow the genetic–environmental interactions that are central to the aetiology of schizophrenia to be captured in a single paradigm.

Genetic models

A plethora of genetic rodent models are being developed, which we discuss below, but it is unrealistic to replicate the complex genetic architecture of schizophrenia in a single rodent model.

Genetic architecture of schizophrenia

Schizophrenia is a polygenic disorder that can be sporadic as well as familial. Many epidemiological studies have shown that genetic factors account for approximately 60–80% of the variance in overall risk[57]. As well as the additive effects of gene networks, interactions between genetic and environmental risk factors have an important role[1].

The genetic architecture of schizophrenia is complex and it is likely that a combination of genetic variants contribute to the risk, including common single nucleotide polymorphism (SNP) alleles that have a small effect, as well as rare coding mutations and copy number variant alleles that have a high penetrance[58]. Estimates suggest that more than 1,000 genes are likely to be involved in the aetiology of schizophrenia[59]. Deep re-sequencing — currently using targeted approaches — of candidate genes, exomes and chromosomal regions, and very-large-scale genome-wide association studies are underway to investigate the many remaining questions surrounding the genetic architecture of schizophrenia.

Ultimately, animal models are needed to address the genetic architecture of the disorder, taking into account both common and rare variants as well as the combination of alleles required to cause the disease, along with the molecular consequences, identified by global mining of the transcriptome and proteome. Clearly, the profound heterogeneity in schizophrenia raises major challenges for modelling the disease in animals. Similarly, it is important to consider interactions between genetic and

γ-oscillations
Oscillatory waves detected in human electroencephalography, with a frequency typically around 40 Hz; thought to be related to consciousness.

Basket cells
A class of GABA (γ-aminobutyric acid)-ergic inhibitory interneurons that innervate the perisomatic region of target neurons. The axonal arborization of basket cells often resembles a basket surrounding the target cell body.

Chandelier cells
A class of GABA (γ-aminobutyric acid)-ergic interneurons of the cerebral cortex that ensheathe the axon initial segment of up to 200 pyramidal cells with cartridge synapses to directly control action potential generation.

Working memory
The active maintenance of limited amounts of information for a short period of time to guide thought processes or sequences of behaviour.

High penetrance
A genetic mutation that has a substantial influence on the risk of disease.

Deep re-sequencing
A technique, typically performed using high-throughput next-generation sequencing, used to obtain the complete nucleotide sequence of a gene or genome that has previously been determined. The term 'deep' refers to the depth, coverage or the number of times an individual nucleotide is sequenced.

Global mining
Non-hypothesis-driven screening of an entire set of biological material, such as the use of microarrays to screen all the RNA from a particular cell type.

environmental factors. Such studies are underway and hold promise[60]; characterizing the complexity of these genetic–environmental interactions to determine the likelihood of developing schizophrenia may be central for establishing translationally valid preclinical models of schizophrenia. In addition, it is vital to use genetic animal models that closely replicate the characteristics of the human genetic variants that contribute to an increased risk of developing schizophrenia, as this would ensure maximal translational validity. Furthermore, understanding the impact of genetic manipulation on neurobiological pathways is crucial for identifying novel targets.

Phenotyping of genetically modified mice

Many genetically modified mice have been developed that target candidate genes (well-characterized and emergent candidate genes) and established pathophysiological mechanisms (for example, glutamatergic and dopaminergic processes). Such mice are providing valuable insight into the neurobiological role of specific genes and neurotransmitters in terms of behavioural phenotypes, as well as the impact of these specific genes and neurotransmitters on downstream biochemical pathways, synaptic function, structural and neuropathological alterations as well as neurodevelopmental processes. Importantly, several candidate genes affect neurotransmitter systems that are considered to be disrupted in schizophrenia (FIG. 1). This convergence adds weight to the utilization of genetically modified mice for translational studies.

It could be argued that studies in genetically modified mice that have rare variants of high penetrance, such as disrupted in schizophrenia 1 (*DISC1*) and the 22q11.2 syntenic region, will hold the most promise for informing on disease mechanisms and hence have utility in drug discovery. However, it is important to remember that schizophrenia is a complex heterogeneous disease and that multiple genes and pathways affect the neural circuitry that underlies the distinct and overlapping symptoms. Commonalities between phenotypes in different genetically manipulated mouse strains may thus be highly informative, as has been previously argued[61]. Therefore, information gained from a range of genetically modified mice, and from other genetic and functional studies, will prove to be valuable in assembling the true neurobiological mechanisms of the disease.

The results of behavioural phenotyping from various genetically modified mice are summarized in TABLE 2. Our criteria for selection was to incorporate genetically modified mice that fall into one of the following three categories: mice expressing modified key candidate genes, based on consistent genetic and molecular evidence (using information from the SchizophreniaGene database meta-analyses)[62]; mouse models based on pathophysiological evidence; and mouse models based on strong systems-led evidence (for example, where a protein encoded by a particular gene is known to affect a biochemical and/or neural pathway that has an established role in the disease). It is notable that the phenotypic characterization of genetically modified mice has typically been conducted using assays such as PPI and locomotor activity, and few studies have used translationally relevant assays for studying cognitive deficits and negative symptoms (TABLE 2). It is clear that PPI and hyperlocomotor activity are not measures of positive symptoms *per se,* yet they have been widely used as predictive screens for antipsychotic compounds.

Numerous genetically modified mice, including those with disruptions in *Disc1*, neuregulin 1 (*Nrg1*) and glutamate-related genes, show altered locomotor activity and deficits in PPI (TABLE 2). Authors often interpret this as a demonstration of schizophrenia-like behaviours. This explanation is an oversimplification, and a more precise interpretation would be that the genetic alteration modifies the neurobiological mechanisms underpinning these behaviours. Given the diversity of the neural systems recruited in PPI[63], it is perhaps not surprising that the disruption of these systems by numerous strategies and genetic alterations can result in PPI deficits. This raises questions about the utility of these phenotypes for drug discovery. Nevertheless, assessing such phenotypes in genetic models does move away from the problems of so-called 'receptor tautology', which is inherent to models in which a dopamine receptor agonist produces behavioural disruptions that are — not surprisingly — restored by dopamine receptor antagonists.

Interestingly, mice with genetic modifications in the dopamine receptor display no overt PPI deficits and no consistent change in a locomotor activity phenotype (TABLE 2). It is possible that compensatory changes, including changes in the expression of other receptors, may mask the expression of a behavioural phenotype. Importantly, clear phenotypes can be revealed following pharmacological challenges, thus providing important mechanistic insight[64]. Hence, a lack of an overt phenotype may not rule out the involvement of a particular gene in regulating a behaviour.

Taken together, this evidence suggests that assays of hyperlocomotor activity and PPI have questionable value in future drug discovery strategies.

Phenotypic assessment of negative symptoms. Few studies have examined negative symptom-like behaviours in mutant models. Anhedonia-like symptoms have been reported in a *Disc1*-modified mouse line (Q31L), as assessed by the forced swim test and sucrose preference test. However, behaviours relating to motivation are likely to be more relevant to the negative symptoms of schizophrenia. In this regard, Kellendock[65] showed that mice overexpressing D2 receptors in the striatum exhibited reductions in lever pressing for food reward in a progressive ratio schedule, which is consistent with impairments in motivation (TABLE 2).

Phenotypic assessment of cognitive symptoms. Many of the genes that are studied in schizophrenia, including *DISC1*, *NRG1* and dystrobrevin binding protein 1 (*DTNBP1*), are present in brain circuitry that is important in cognition, and the proteins encoded by these genes are often functionally linked to glutamatergic synapses (FIG. 1). Given that glutamatergic neurotransmission is fundamental to synaptic plasticity and cognition, it is evident that schizophrenia-related genes are likely to affect cognitive

22q11 syntenic region
Synteny describes the preservation of colocalized genes on chromosomes in different species. Mouse genes that are orthologous to the human genes that map onto human chromosome 22q11 are grouped together on mouse chromosome 16.

Progressive ratio schedule
A schedule in which the number of responses a subject is required to make to obtain a reinforcement (such as a food reward) increases progressively. A typical performance measures the ratio at which responding ceases for a predefined period, which may be related to the subject's motivational state.

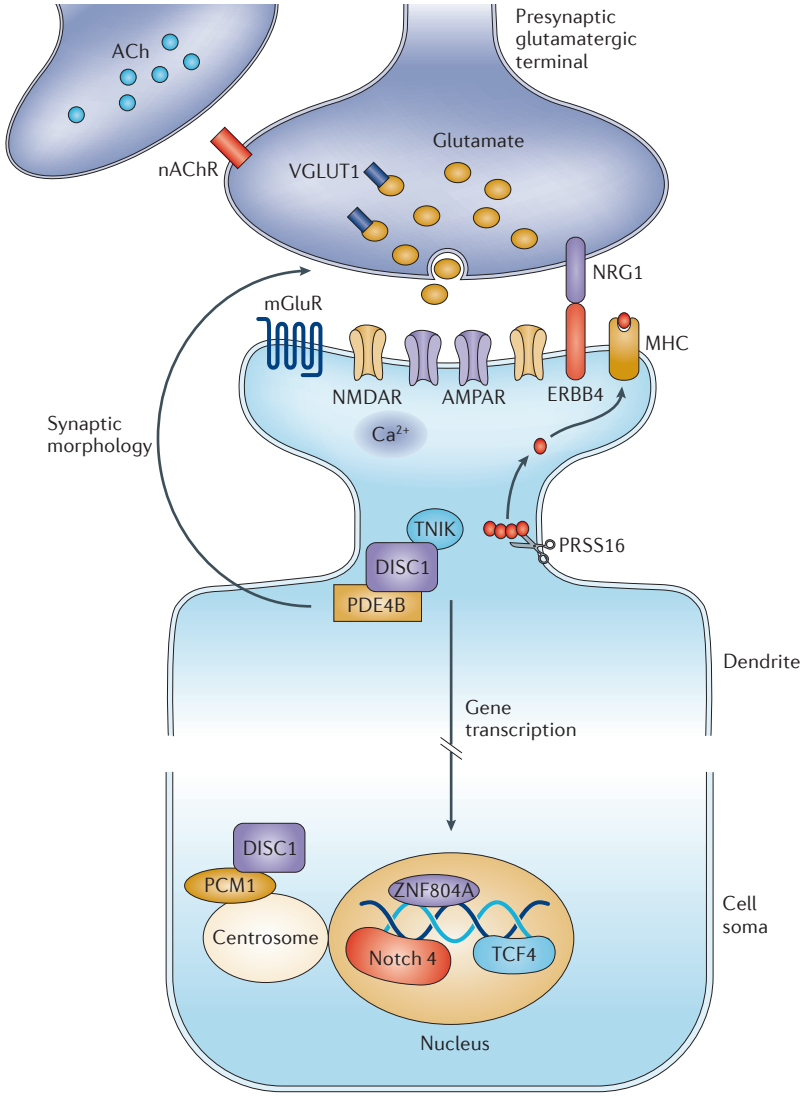

Figure 1 | **Genes implicated in schizophrenia converging at the synapse and nucleus.** The schematic representation shows the functional relationship between some of the most prominent genes that are implicated in the aetiology of schizophrenia. Many of these genes are involved in glutamate synapse function. In particular, disrupted in schizophrenia 1 (DISC1) forms a complex with phosphodiesterase 4B (PDE4B) and TNIK (TRAF2 and NCK-interacting kinase) to coordinate signalling pathways that regulate synaptic structure and gene transcription. Similarly, neuregulin 1 (NRG1)–ERBB4 signalling regulates synapse morphology and function. The α7 subunit-containing nicotinic acetylcholine receptors (nAChRs), which are strongly implicated in disease risk via gene copy number variations, are located on presynaptic glutamatergic terminals. Major histocompatibility complex (MHC) molecules have some role in the maintenance and plasticity of synaptic connections, but this is currently not well characterized. At the nucleus, a proteolytic product of Notch 4 is a transcriptional regulator, as are transcription factor 4 (TCF4) and zinc finger protein 804A (ZNF804A). The perinuclear centrosome acts as a microtubule-organizing centre and has a well-established role in mitosis. Its function in post-mitotic neurons remains unclear but it has been proposed to have a role during neuronal development and migration. Pericentriolar material 1 (PCM1) sequence variations may represent one of the greatest genetic influences currently reported on the risk of developing schizophrenia. Genes have been selected based on information from the Schizophrenia Gene database meta-analyses[62]; DISC1 interactions have been covered in detail in REF. 136. AMPAR, AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor; mGluR, metabotropic glutamate receptor; NMDAR, NMDA (*N*-methyl-D-aspartate) receptor; PRSS16, serine protease 16; VGLUT1, vesicular glutamate transporter 1.

processes. Understanding how the disruption of specific genes affects discrete cognitive processes is paramount for the success of future drug discovery strategies.

Although assays for cognitive testing in genetically modified mice require further optimization to increase their translational relevance, there are some tasks that are homologous to human constructs and that recruit prefrontal circuitry; these include the ASST and the 5-CSRTT. As such, they provide a good starting point for cognitive phenotyping in genetically modified mice and have great potential in drug discovery. To date, however, there are only isolated studies in which genetically modified mice have been assessed in cognitive tasks. Instead, rather broad behavioural phenotypes have been assessed, which have methodological confounds and are subject to interpretational caveats (TABLE 2).

Nevertheless, the role of glutamate receptor subtypes is being investigated in a rigorous manner. For example, Bannerman's group[66,67] report that knockout mice deficient in AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor 1 (GluR1 (also known as GluA1); *Gria1*$^{-/-}$ mice) and in the NMDA receptor (NR2A (also known as GluN2A); *Grin2a*$^{-/-}$ mice) display hippocampal-dependent deficits in working memory but not in reference memory. Furthermore, region-specific, inducible and reversible knockout mice with altered expression of the NR1 subunit of the NMDA receptor (NR1 (also known as GluN1); *Grin1*$^{-/-}$ mice) have also been constructed. Findings from these mice are beginning to reveal the regional and temporal contributions of NMDA receptors in constructs of cognition more precisely[68].

It should also be recognized that cognitive deficits are common to many neurological and psychiatric disorders; however, it is not known whether these defects result from the same disrupted neurobiological mechanisms and brain circuitry. Hence, the impact of genetic manipulation on behaviour alone will not necessarily be sufficient to understand whether convergent and divergent mechanisms exist across a range of neuropsychiatric and neurological disorders. Other approaches, incorporating functional brain imaging and electrophysiology, should shed light on the distinct process involved.

Finally, it should be highlighted that a plethora of data have been published that have minimal translational relevance owing to the confounding factors associated with rodent behavioural assays (for example, the fact that the cognitive task may not measure the same human construct, or that a cognitive task can be sensitive to interference by effects such as low motivation or sedation; BOX 3) as well as factors associated with the use of genetically modified mice themselves (for example, the background strain; BOX 5). Often, it has been claimed that genetically modified mice exhibit a schizophrenia-like behavioural phenotype, yet the evidence presented is subject to confounding factors that cloud this interpretation (BOX 5).

Drug evaluation in genetic mouse models

Despite the availability of a considerable amount of data on the behavioural phenotyping of mouse models of risk genes for schizophrenia (TABLE 2), there are limited

Table 2 | **Behavioural phenotyping of genetically modified mice***

Mouse model (genetic modification)	Novelty-induced LMA	PPI	Anhedonia and avolition tests	Sociability, social novelty and social interaction	Spatial working and short-term memory	Refs
Candidate gene-related: DISC1						
Q31L homozygotes (amino acid substitution)	×	Ambiguity‡	Ambiguity‡ in FST ✓ in SPT; ND in other study	Ambiguity‡	Ambiguity‡ in DNMP	69,72
L100P homozygotes (amino acid substitution)	Ambiguity‡	Ambiguity‡	× in FST × in SPT; ND in other study	× (in both studies)	Ambiguity‡ in DNMP	69,72
Disc1-truncated hemizygotes and homozygotes	×	×	ND	ND	✓ in DNMP	137,138
Dominant negative *Disc1*-truncated hemizygotes	×	ND	✓ in TST	ND	ND	73
Dominant negative *Disc1*-truncated hemizygotes (truncated carboxy-terminal with CaMKIIα promoter)	✓	✓	✓ in FST	×	× in SA	139
In utero Disc1 shRNA knockdown	×	✓	× in FST	ND	✓ in DNMP	140
Disc1-truncated (inducible promoter)	× (✓ in males only)	×	× in FST (✓ in females only) × in TST	× (✓ in males only)	× in SA	141,142
Disc1-truncated (transient expression induced on postnatal day 7; inducible promoter)	ND	ND	✓ in FST	✓	✓ in DNMP	143
Disc1 knockout mice (*Disc1*$^{\Delta 2-3/\Delta 2-3}$ mice)‡	×	✓	× in FST	× (sociability increased)	× in SA × in RAM	144
Candidate gene-related: NRG1						
Nrg1$^{+/-}$ knockout mice	✓	✓	ND	ND	ND	145
Nrg1$^{+/-}$ type III knockout mice (CRD isoform)	×	✓	ND	ND	✓ in DNMP	146
Nrg1$^{+/-}$ type I, II and III knockout mice (transmembrane domain)	ND	ND	ND	✓	× in SA	147
Gandidate gene related: ERBB4 (neuregulin receptor); DISC1-related; chromosome 22q11.2						
Erbb4$^{+/-}$ knockout mice	✓	×	ND	ND	ND	145
Erbb4$^{+/-}$ and *Erbb4*$^{-/-}$ knockout mice	× (LMA reduced)	ND	ND	ND	ND	148
Erbb2/b4$^{-/-}$ CNS knockout mice	×	✓	ND	ND	ND	149
PV-Cre; *Erbb4*$^{-/-}$ knockout mice	✓	✓	ND	ND	✓ in RAM	77
Pde4b$^{-/-}$ knockout mice (*Disc1* interactor)	× (LMA reduced)	✓	✓ in FST	ND	ND	150
Pafah1b1$^{+/-}$ knockout mice (*Disc1* interactor)	×	×	ND	ND	ND	151
Human chromosome 22q11.2 sytenic deletion (*Df (16)A*$^{+/-}$ mice)§	ND	ND	ND	ND	✓ in DNMP	105
Human chromosome 22q11.2 sytenic deletion (*Lgdel*$^{+/-}$ mice)§	×	✓	ND	ND	ND	152
Human chromosome 22q11.2 syntenic deletion (*Df1*$^{+/-}$ mice)§	×	✓	ND	ND	ND	153

examples of pharmacological studies in the most investigated candidate gene models (TABLE 3).

Notably, the most widely assessed behavioural phenotypes are PPI and locomotor activity. Notwithstanding the limitations of these tasks, examination of two *Disc1*-mutant mouse models has revealed differences in sensitivity to antipsychotic drugs during the rescue of PPI deficits. Clozapine and haloperidol partially reversed a

Table 2 (cont.) | **Behavioural phenotyping of genetically modified mice***

Mouse model (genetic modification)	Novelty-induced LMA	PPI	Anhedonia and avolition tests	Sociability, social novelty and social interaction	Spatial working and short-term memory	Refs
Dopamine-related						
Drd1a$^{-/-}$ knockout mice	×	ND	ND	ND	ND	154
Drd1$^{-/-}$ knockout mice	✓	ND	ND	ND	ND	155
Drd2$^{-/-}$ knockout mice	× (LMA reduced)	× (PPI reduced)	ND	ND	ND	156,157
Drd2-transgenic mice (inducible *Drd2* overepxression)	×	×	✓ in ProgR	ND	✓ in RAM ✓ in DNMP	65,158
Comt$^{-/-}$ and *Comt*$^{+/-}$ knockout mice	×	×	ND	×	✓ in SA	159,160
Slc6a3$^{-/-}$ knockout mice (DAT)	✓	✓	ND	✓	× in MWM‖ ✓ (impaired adaption)	75,161, 162
Glutamate-related						
Grin1$^{-/-}$ knockdown mice (NR1)	✓	✓	ND	✓	ND	163,164
Grin2$^{-/-}$ knockout mice (NR2A)	✓	×	× in FST	ND	✓ in RAM ✓ in DNMP × in MWM‖	67,165, 166
Gria1$^{-/-}$ knockout mice (GluR1)	✓	✓	× in SPT	✓	✓ in RAM	167–169
Gria4$^{-/-}$ knockout mice (GluR4)	×	✓	ND	×	× in DNMP	170
Ppp1r2-cre$^{+/-}$*/NR1*$^{loxP/loxP}$ ablation of NR1 receptors in GABA interneurons	✓	✓	✓ in SPT	✓	✓ in SA	171
Slc17a7$^{+/-}$ knockout mice (VGLUT1)	×	ND	✓ in FST ✓ in SPT	ND	ND	172,173
Akt1$^{-/-}$ knockout mice	×	✓	✓ in TST	ND	× in SA	174,175
Dtnbp1$^{-/-}$ knockout mice	✓	× (PPI enhanced)	ND	ND	✓ in DNMP (operant chamber and T maze)	176–179

✓, disease-relevant phenotype detected; ×, no disease-relevant phenotype detected; +/–, heterozygote for gene disruption; –/–, homozygote for gene disruption; CaMKIIα, calcium/calmodulin-dependent protein kinase IIα; CNS, central nervous system; COMT, catechol-*O*-methyltransferase; CRD, cysteine-rich domain (present in some NRG1 isoforms); DISC1, disrupted in schizophrenia 1; DNMP, delayed non-match to place test (T maze); DRD1A, dopamine receptor D1A; FST, forced swim test; GABA, γ-aminobutyric acid; GRIA1, AMPA-selective glutamate receptor 1; GRIN1, NMDA receptor subunit NR1; LMA, locomotor activity; MWM, Morris water maze task; ND, not determined; NMDA, *N*-methyl-D-aspartate; NRG1, neuregulin 1; PAFAH1B1, platelet-activating factor acetylhydrolase 1b regulatory subunit 1; PDE4B, phosphodiesterase 4B; PPI, prepulse inhibition; PPP1R2, protein phosphatase inhibitor 2; ProgR, progressive ratio schedule; PV-Cre, mice expressing Cre recombinase under the control of the parvalbumin gene promoter RAM, radial arm maze; SA, spontaneous alternation (T maze); shRNA, short hairpin RNA; SLC6A3, solute carrier 6 member 3 (also known as DAT; dopamine transporter); SPT, sucrose preference test; TST, tail suspension test; VGLUT1, vesicular glutamate transporter 1 (also known as SCL17A7). *Of the strains shown, genetically modified *Disc1* mice are among the few to be evaluated for latent inhibition; the point mutants and the mutant mice expressing a carboxy-terminal truncated form of *Disc1* under the CaMKIIα promoter showed schizophrenia-related deficits in this task[69]. *Drd2*-overexpressing mice appear to be the only strain tested for executive function (attentional set-shifting and reversal learning); the mutants showed mild deficits in reversal trials but not in schizophrenia-related extradimensional–intradimensional deficits in this task. Approaches in which region-specific deletions in genetically modified mice are utilized are generally not shown here. For example, deletion of NR1 subunits in subregions of the hippocampus revealed regionally specific roles in spatial memory tasks[68], and NR1 subunit ablation on parvalbumin-positive interneurons impaired working memory in the T maze task[180]. ‡'Ambiguity' refers to evidence both for and against a disease-relevant phenotype. §*Disc1*$^{\Delta 2-3/\Delta 2-3}$ mice are *Disc1*-mutant mice lacking exons 2 and 3 of the *Disc1* gene owing to a targeted disruption of *Disc1* exons 2 and 3. *Df(16)A*$^{+/-}$, *Lgdel*$^{+/-}$ and *Df1*$^{+/-}$ mice are mutant mice with deletions of mouse chromosome 16, which models a microdeletion on human chromosome 22q11.2 in velocardiofacial syndrome, DiGeorge syndrome and 22q11 deletion syndrome developmental disorders ('Lgdel' refers to a larger deletion). ‖For the MWM, results are presented for working memory but not reference memory paradigms.

Human constructs
In relation to cognition, human constructs are specific elements of mental processes, such as attention, memory, producing and understanding language, solving problems and making decisions.

Reference memory
Also known as long-term memory. In rodents this typically involves reference to external cues, which is needed for succesful completion of tasks such as finding a hidden platform in the Morris water maze.

severe PPI deficit and increased locomotor activity in *Disc1*-mutant mice with the L100P mutation but had no effect on a weaker PPI deficit in *Disc1* mutants with the Q31L mutation. In the forced swim test, *Disc1* mutants with the Q31L mutation exhibited a 'depressed' phenotype that was reversed by the monoaminergic drug bupropion, whereas *Disc1* mice with the L100P mutation did not exhibit deficits in this test. These findings led the authors to conclude that *Disc1* missense mutations can lead to distinct phenotypes that are related to depression and schizophrenia, and that these phenotypes are dependent on the localization of the alterations in the *Disc1* gene. Further pharmacological probing with inhibitors of phosphodiesterase 4B and glycogen synthase kinase suggested that the expression of a range of schizophrenia-like behaviours involves the interaction of DISC1 with phosphodiesterase 4B and glycogen synthase kinase[69,70].

However, recent studies — in which minimal behavioural phenotypes have been observed — question the validity of these findings[71,72]. Mounting evidence suggests that the observed phenotypes could potentially have been the result of inadequate backcrossing of the mice, and thus the phenotypes could have been influenced by the genetic background instead of being attributable to the *Disc1* missense mutation *per se*. Furthermore, the direct translational relevance of the genetic mutation present in these animals to the mutation present in patients with schizophrenia (the *DISC1* mutation; a T1q43;11q21 translocation) is arguably weaker than that of more

Box 5 | **Interpreting data from genetic mouse models: confounding factors**

The main confounding factors in the interpretation of findings from genetic mouse models are the effects of the background strain, neurodevelopment and interactions between genetic and environmental factors. Some background strains have altered levels of emotionality and a different cognitive profile compared to other strains[135]. Hence, the role of the mutation or genetic variation under investigation may be masked by the effects of the background strain. Altering a gene (for example, by knocking it out) throughout the developmental period may result in the induction of compensatory processes that in turn may cloud the effects of the mutation under investigation. Furthermore, housing conditions and stress responses (either through the housing environment or the behavioural test itself) may interact with the gene of interest, resulting in a phenotype reflecting a genetic–environmental interaction rather than simply a single-gene mutation. Clearly, these 'gene–environment' phenotypes are of considerable importance from a disease perspective but it is important to understand the mechanisms underlying genetic–environmental interactions from a neurobiological perspective.

Interpretation of data generated from behavioural tasks also necessitates careful consideration of potential confounding factors. These are often not given the attention they deserve. Teasing out the relevant component from the many factors that can affect a behavioural output requires several approaches, many of which cannot be measured in a single test. For example, deficits in executive control can affect attention, long-term memory and working memory. Similarly, an inability to encode associations between a stimulus and a reward may affect an animal's ability to perform goal-directed behaviours. Hence, an apparent anhedonic phenotype may in fact be due to aberrant encoding of information. Clearly, sensory impairments may also affect a range of behavioural outcomes. For example, potential confounding factors such as hearing loss and startle reactivity are important considerations in the evaluation of a prepulse inhibition phenotype.

recently developed genetically modified *Disc1* models[73]. Exactly how a risk mutation is modelled is also crucial. Indeed, opposing effects of *Disc1* manipulation on neuronal growth and maturation have been observed[46,74], raising questions about which targets are most appropriate in drug discovery.

Antipsychotic drugs have varying abilities to reverse PPI deficits in genetically modified mice in which the region sytenic to human chromosome 22q11 is disrupted, or mice in which *Nrg1*, *Erbb4* (also known as *Her4*), *Akt1* or genes encoding NMDA receptors have been disrupted (TABLE 3). Interestingly, this is in stark contrast to the clear rescue of PPI and locomotor hyperactivity by various antipsychotic drugs in dopamine transporter (DAT; also known as SLC6A3) knockout mice[75,76]. This may be reconciled by the fact that DAT knockout mice exhibit marked dopaminergic dysregulation, which is likely to be rescued by antipsychotic drugs acting via D2 receptors. It is probable that the genetic alterations in 'schizophrenia-related genetically modified mice' do not disrupt the dopaminergic system to the same degree, and other neurobiological pathways are affected. Alternatively, variations in the background strain and testing conditions may account for these differences.

The extent to which pharmacological agents rescue a given behavioural phenotype in a mouse model may also be confounded by other nonspecific effects of the drugs. For example, clozapine has a sedative effect at doses in excess of 1 mg per kg, and this may explain the putative reversal of hyperlocomotion rather than a specific reversal of gene-induced hyperlocomotion. Similarly, without an interaction between the drug and the genotype in the analysis, it is difficult to conclude whether a drug is reversing a distinct phenotype, and the finding that a drug reduces schizophrenia-like behaviour to a similar degree in both mutated and wild-type mice should be interpreted with caution.

Pharmacological agents have been used to probe the neurotransmitter systems involved in a phenotype. For example, Wen *et al.*[77] demonstrated that the GABAergic positive allosteric modulator diazepam rescued PPI deficits in mice in which *Erbb4* had been ablated in parvalbumin-positive GABAergic interneurons. This, along with neurochemical and electrophysiological evidence, provided greater insight into the role of NRG1 in neural transmission. These approaches are therefore necessary to provide mechanistic insights into the role of neurotransmitter systems in models with particular genetic manipulations.

In summary, there have been limited drug discovery studies using genetically modified mouse models, and most studies have focused on using assays that have questionable translational relevance. Although some proof-of-concept studies have been conducted using existing antipsychotic drugs (for example, clozapine and haloperidol) in mutated mice exhibiting deficits in PPI and locomotor activity, there are a dearth of studies investigating compound rescue in genetically modified mice exhibiting negative symptoms and cognitive deficits. Nevertheless, a recent study demonstrated that a 5-HT_{2C} receptor antagonist, but not haloperidol (as predicted), increased motivation in mice in which the D2 receptor is overexpressed — these mice are reluctant to work for rewards[78]. This study is encouraging as it suggests that drug-induced rescue is possible in a behavioural assay that has translational relevance to the negative symptoms of schizophrenia.

Assessing compound-induced rescue in genetically modified mice that exhibit translationally relevant schizophrenia-like behaviours provides a major opportunity for future drug discovery. However, harmonization of behavioural phenotyping strategies across laboratories is crucial. Furthermore, rigorous pharmacological analysis of test compounds in clearly defined genetic phenotypes is necessary to obtain results that can be met with confidence.

L100P mutation
A genetic modification induced by *N*-ethyl *N*-nitrosourea mutagenesis in the mouse disrupted in schizophrenia 1 (*Disc1*) gene, whereby an adenine to thymine nucleotide transition causes the amino acid at position 100 of the DISC1 peptide to change from a leucine to a proline.

Q31L mutation
A genetic modification induced by *N*-ethyl *N*-nitrosourea mutagenesis in the mouse disrupted in schizophrenia 1 (*Disc1*) gene, whereby a thymine to cytosine nucleotide transition causes the amino acid at position 31 of the DISC1 peptide to change from a glutamine to a leucine.

Table 3 | **Drug reversal studies in genetically modified mice exhibiting schizophrenia-related behavioural deficits**

Gene	Genetic modification	PPI impairment	Hyperlocomotor activity	Forced swim test	Sociability or social novelty	Latent inhibition deficit	Refs
Disc1	L100P (ENU mutant)	Partial reversal by haloperidol and clozapine; reversal with rolipram (a PDE4B inhibitor) and with combined subthreshold doses of rolipram and a GSK3 inhibitor (TDZD-8)	Reversed by haloperidol and clozapine as well as with combined subthreshold doses of rolipram and TDZD-8	ND (mutant mice unaffected)	ND (mutant mice unaffected)	Reversed by haloperidol and clozapine	69,70, 181
Disc1	Q31L (ENU mutant)	Reversed by bupropion and TDZD-8 but not by clozapine, haloperidol or rolipram	ND (locomotor activity unaffected in mutant mice)	Reversed by TDZD-8 and bupropion but not by rolipram	Reversed by TDZD-8	Not reversed by clozapine	69,70
Disc1	*In utero* *Disc1* shRNA knockdown	Reversed by clozapine	ND (locomotor activity unaffected by *Disc1* knockdown)	ND (unaffected by *Disc1* knockdown)	ND	ND	140
Nrg1	*Nrg1*$^{+/-}$ type III knockout mice (CRD isoform)	Reversed by chronic nicotine administration	ND	ND	ND	ND	146
Nrg1	*Nrg1*$^{+/-}$ knockout mice	Not reversed by clozapine	Reversed by clozapine	ND	ND	ND	145
Erbb4	*Erbb2/b4*$^{-/-}$ CNS knockout mice	Reversed by clozapine	ND	ND	ND	ND	149
Akt1	*Akt1*$^{-/-}$ knockout mice	Female knockout mice exhibit PPI deficits; partial reversal by 8-OH DPAT (a 5-HT$_{1A}$ receptor agonist) and SB21673 (a GSK3 inhibitor) but not by raclopride or clozapine	ND	ND	ND	ND	174

Intermediate phenotypes

A promising approach for drug discovery is to assess compounds in translational behavioural assays in animal models that have improved construct validity. The recent development of genetic mouse models, along with improved behavioural methods for assessing disease-related phenotypes, is encouraging from this perspective. In particular, the identification of rare genetic variants that dramatically increase the risk of developing schizophrenia will facilitate the development of rodent models with high construct validity. There are however, some important gaps that need to be filled if we are to overcome the current translational bottleneck.

It is imperative to gain knowledge of the neural circuitry and neurophysiological mechanisms underpinning the symptoms of schizophrenia, and how genetic variation affects neural systems to predispose individuals to specific disease symptoms. These so-called intermediate phenotype- (or endophenotype)-based approaches are capturing much attention[79,80]. In essence, intermediate phenotypes can be viewed as measurable components along the pathway between a defined risk factor (for example, environmental or genetic) and the clinical syndrome (the phenotype). Intermediate phenotypes may provide insight into the mechanisms underlying the disease, and thereby give greater confidence for successful drug targeting. Nevertheless, one of the major challenges is to map and/or align intermediate phenotypes onto specific symptoms of schizophrenia, and to determine which of those intermediate phenotypes are most predictive for remediation by drugs.

Here, we review evidence from neuronal circuitry-based imaging and electrophysiological approaches to discuss how the application of these strategies in preclinical models is showing signs of success for future drug discovery. We also argue that combining these approaches into integrated models will enable us to accelerate the drug discovery process.

Imaging the dysfunctional brain

Extensive structural (diffusion tension imaging) and functional brain imaging studies such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have provided clear evidence for abnormalities in schizophrenia (FIG. 2). Altered activity in the prefrontal cortex has been correlated with various cognitive deficits and can be manifested as hypofrontality (reduced cerebral blood flow and metabolism) or hyperfrontality (increased cerebral blood flow and metabolism), depending on the task that the patient is asked to complete. The current view is that dysfunction of the prefrontal cortex in patients with schizophrenia is more complex than simply showing 'increased' or 'decreased' activity[81], and that either hypo- or hyperfrontality may manifest, both of which represent prefrontal cortex inefficiency[82].

Of course, the prefrontal cortex does not function in isolation from other regions of the brain, and dynamic interactions with other neural systems are crucial for information processing and the manifestation of symptoms. Measuring how neurons communicate with each other in a dynamic way, at the regional level and in terms of local circuitry, has — until recently — been a major challenge.

Table 3 (cont.) | **Drug reversal studies in genetically modified mice exhibiting schizophrenia-related behavioural deficits**

Gene	Genetic modification	PPI impairment	Hyperlocomotor activity	Forced swim test	Sociability or social novelty	Latent inhibition deficit	Refs
Erbb4	PV-Cre; *Erbb4*$^{-/-}$ knockout mice	Attenuated by diazepam	ND	ND	ND	ND	77
Chromosome 22q11 deletion	Overexpression of four genes from human chromosome 22q11	Haloperidol and clozapine (at acute and chronic doses) restore sensitized hyperactivity	ND	ND	ND	ND	182
Grin1 (NR1)	*Grin1*$^{-/-}$ knockdown	Haloperidol, quetiapine, olanzapine and risperidone enhance PPI in wild-type and *Grin1*$^{-/-}$ mice; inconsistent results with clozapine between studies	Attenuated by clozapine and olanzapine; conflicting results with haloperidol	ND	Restored by clozapine but not by haloperidol	ND	163, 183–185
Grin2 (NR2)	*Grin2*$^{-/-}$ knockout mice	ND	Attenuated by haloperidol and risperidone	ND	ND	ND	165
Gria1 (AMPA receptor 1)	*Gria1*$^{-/-}$ knockout mice	ND	Attenuated by haloperidol and lithium but not by SB216763	ND	ND	ND	66,169
Grm1 (mGluR1)	*Grm1*$^{-/-}$ knockout mice	PPI deficits reversed by lamotrigine but not raclopride	ND	ND	ND	ND	186
Grm5 (mGluR5)	*Grm5*$^{-/-}$ knockout mice	PPI deficits not reversed by lamotrigine, clozapine or raclopride	ND	ND	ND	ND	187
Slc6a3 (DAT)	*Slc6a3*$^{-/-}$ knockout mice	Reversed by D2- and 5-HT$_{2A}$receptor antagonists, fluoxetine, raclopride, clozapine and quetiapine; no effect of D1 receptor antagonist SCH23390	Inhibited by raclopride, SCH23390,5-HT$_{2A}$ receptor antagonists, 5-HT receptor agonists, ampakines, nicotine, lithium, valproate and GSK3β inhibitors	ND	ND	ND	75,76

5-HT$_{1A}$, 5-hydroxytryptamine receptor 1A; 8-OH DPAT, 7-(dipropylamino)-5,6,7,8-tetrahydronaphthalen-1-ol; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; CNS, central nervous system; D1, dopamine receptor D1; DISC1, disrupted in schizophrenia 1; ENU, *N*-ethyl-*N*-nitrosourea; GRIA1, AMPA receptor 1; GRIN1, NMDA receptor subunit NR1; GSK3, glycogen synthase kinase 3; mGluR1, metabotropic glutamate receptor 1; ND, not determined; NMDA, *N*-methyl-D-aspartate; NRG1, neuregulin 1; PDE4B, phosphodiesterase 4B; PPI, prepulse inhibition; PV, parvalbumin; shRNA, short hairpin RNA; SLC6A3, solute carrier 6 member 3 (dopamine transporter).

One limiting factor in elucidating altered brain functioning at a systems level has been the limited application of available computational modelling algorithms to translational brain imaging data. For example, although algorithms aimed at elucidating alterations in regional and neural systems connectivity have long been used in clinical brain imaging[83–85], they have only been applied to a limited degree in a preclinical context[86].

The application of techniques to measure the functional connectivity of brain regions to preclinical imaging data and drug discovery is in its infancy. Recently, we applied[87] partial least squares regression to data generated from 2-deoxyglucose (2-DG) imaging to investigate the functional connectivity between regions of the brain in rats treated with subchronic doses of PCP. 2-DG imaging, which is broadly equivalent to PET imaging in humans, has been widely used to investigate the effects of diverse experimental manipulations (for example, pharmacological and genetic manipulation) on function-related changes in regional glucose use. Importantly, this study revealed schizophrenia-related alterations in the functional connectivity of the prefrontal cortex with other regions of the brain, and also confirmed the previously established hypofrontality and hypometabolism in the reticular thalamus following repeated PCP treatment[88].

A key advance is the integration of CNTRICS-approved cognitive behavioural measures with brain imaging approaches. Our study[87] was the first of its kind to demonstrate that modafinil restores PCP-induced deficits in the ASST; in parallel, it also restores PCP-induced hypofrontality and enhances the functional connectivity of the prefrontal cortex with the locus coeruleus. These findings closely align with clinical imaging and cognitive studies of modafinil[89–91], and demonstrate the forward and reverse translational relevance of these two approaches. Hence, combining these translational behavioural and imaging methodologies with a validated disease model[88,92,93] provides a powerful means of gaining a mechanistic understanding of drug action at the level of neural circuitry, and for progressing new targets through the drug discovery process.

A further advance will be the adoption of algorithms from network science to understand how the properties of brain networks are affected in disease models that have

Partial least squares regression
A multivariate modelling method that is useful for quantitatively defining the relationship between several collinear predictors and response variables. In neuroimaging it has been used to define functional connectivity between regions of the brain.

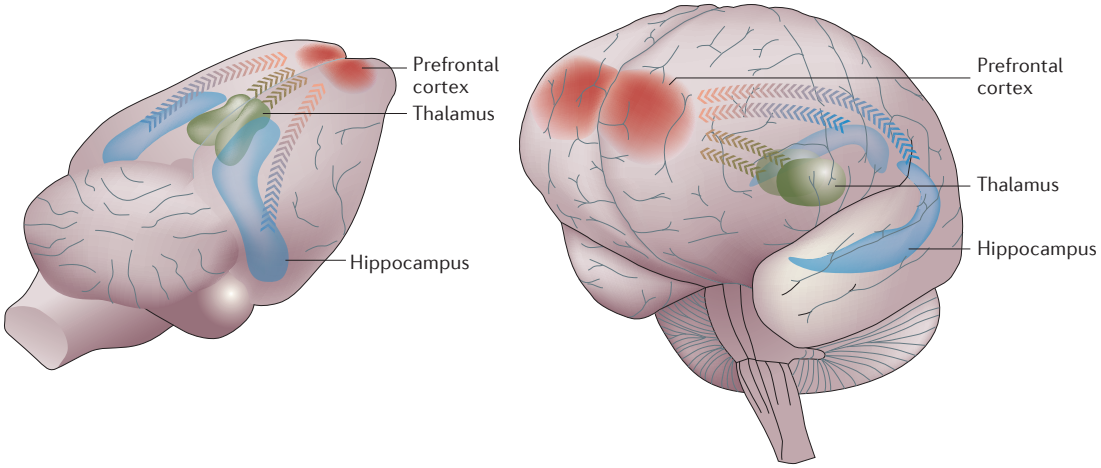

Figure 2 | **Dysfunctional connectivity in schizophrenia.** Aberrant activity in both rodent models of the disease (left panel) and in patients (right panel) is centred on prefrontal–hippocampal–thalamic networks.

construct validity. These algorithms enable the objective characterization of alterations in functional brain network connectivity on multiple scales: ranging from regional alterations to alterations in neural systems as well as alterations that are seen in global network properties[94]. Exciting findings from this research demonstrate that the human brain has properties in common with other complex networks (such as the Internet) that support an efficient transfer of information. Brain imaging studies (such as fMRI) have revealed that these small-world properties are altered in schizophrenia[95–97]. These abnormalities in the organization of brain networks are consistent with aberrant brain development but as yet it is unclear how networks form during development, and when and how they become perturbed in individuals who are at a high risk of developing schizophrenia.

These algorithms have been applied to functional brain imaging data obtained from a rodent subchronic PCP treatment model, and they demonstrate that the alterations in functional brain network structure at a global scale in this translational model are similar to those observed in patients with schizophrenia[98].

The application of these technologies to drug discovery is eagerly awaited. The current idea that drugs act in particular regions of the brain is overly simplistic, and it is unlikely that the clinical efficacy of all drugs can be established solely based on their ability to reverse regional deficits in cerebral metabolism. The ability to understand how a drug is able to reconstruct network activity in a dysfunctional brain offers immense promise for identifying compounds that are likely to be successful in the clinic. Implementing this approach in preclinical studies, using models of construct validity, is likely to reduce attrition in late stages of drug development.

Mechanisms of dysfunctional network activity

Communication between areas of the brain is manifested in patterns of synchronized and desynchronized neuronal activity that can be detected by local field potentials and electroencephalogram recordings.

Of particular interest to schizophrenia are neural oscillations in the θ (4–7 Hz) and γ (30–100 Hz) frequencies. Importantly, fast spiking parvalbumin-positive GABAergic interneurons have been shown to be central to the mechanisms of θ- and γ-generation[99–101]. Hence, dysfunction of parvalbumin-positive interneurons could potentially cause dysfunctional network activity. Importantly, in schizophrenia there is both pathological and electrophysiological evidence to support the disruption of GABAergic cells. Studies have shown that the expression of GABAergic markers, including parvalbumin in post-mortem brain samples[41], is reduced in schizophrenia; clinical studies have also shown alterations in the characteristics of spontaneous γ- and θ-oscillations in the prefrontal and temporal cortices, which have been correlated with several symptoms of schizophrenia[102,103]. However, the extent to which impairments in GABAergic interneurons contribute to the clinical symptoms of schizophrenia remains to be established.

Deficits in GABAergic interneurons have been demonstrated in NMDA receptor models and genetic models relevant to schizophrenia[104]. The expression of GABAergic markers such as parvalbumin is reduced following subchronic and chronic PCP treatment as well as in a *Disc1*-transgenic mouse model of schizophrenia[73,88]. Interestingly, clozapine (but not haloperidol) reverses the parvalbumin deficit induced by repeated PCP treatment, but clozapine does not rescue the parallel changes in hypofrontality. This suggests that hypofrontality can be sustained in the absence of GABAergic basket cell and/or chandelier cell dysfunction in the prefrontal cortex. In future studies it would be beneficial to determine whether γ- and θ-oscillations are disrupted in these genetic and pharmacological models and, if so, to examine the ability of drugs to rescue these deficits.

Encouragingly, mice that model deletion of human chromosome 22q11 have deficits in prefrontal–hippocampal synchrony that appear to be related to performance in a working memory task[105], but drug reversal studies have not yet been conducted. The importance of

examining synchrony between key regions of the brain and neural circuits, particularly their relationship to behaviour, cannot be understated. Of particular interest is the examination of thalamocortical synchrony and activity in the cingulate cortex and the reticular nucleus of the thalamus.

In summary, recent technological advances have enabled us to gain greater insight into the cellular mechanisms that underlie the network dysfunction that is relevant to schizophrenia. Furthermore, the ability to measure network oscillations using next-generation electrophysiology in freely moving and behaving animals provides us with more sophisticated methods to investigate brain dysfunction in disease models that exhibit construct validity. This approach could prove to be an effective strategy for identifying novel therapeutic agents to treat schizophrenia.

Integrating genetic and neural systems data

Thousands of genes regulate the formation of brain circuitry during development, acting in a complex and synergistic fashion to govern the expression of neuropsychiatric phenotypes. It is probable that many genetic mutations converge on particular neural circuitry that is related to defined symptoms.

Imaging genetics is an emerging field that combines the analysis of genetic variation with quantification of structural and functional abnormalities in the live human brain. The application of neuroimaging techniques, frequently in conjunction with a cognitive test, is producing intriguing evidence that candidate genes may affect network function in schizophrenia[106,107]. Several candidate genes have been linked to structural and functional changes in the brain (measured by MRI) that are relevant to schizophrenia; these include the genes enoding catechol-*O*-methyltransferase (*COMT*)[108], metabotropic glutamate receptor 3 (*GRM3*)[109], potassium voltage-gated channel subfamily H member 2 (*KCNH2*)[110], *DISC1* (REF. 111), glutamate decarboxylase 1 (*GAD1*; also known as *GAD67*)[112], *NRG1* (REF. 113) and zinc finger protein 804A (*ZNF804A*)[114].

These studies are often conducted in healthy individuals, in whom phenotypic variability is likely to be lower than in patients with schizophrenia. In an innovative study, this has been extended to genome-wide SNP analysis, using individuals stratified by fMRI as a quantitative phenotype. This approach has revealed a small number of genes with a potential role in the activation of the prefrontal cortex[115,116].

However, questions remain over the validity of these studies owing to their small sample sizes, lack of replication and the genetic heterogeneity of the individuals enrolled in the study. The influences of genetic variation on brain structure in the genes studied to date is thought to be subtle[117,118].

In summary, the influence of genetics on the development of schizophrenia may be most clearly identified using a combination of imaging and cognitive studies. This in turn suggests that translational animal models, particularly those involving a genetic component, might advantageously adopt equivalent methodological paradigms to provide intermediate phenotypes and biomarkers that can be used in drug discovery and to monitor drug efficacy in humans.

Conclusion

The discovery of drugs for treating schizophrenia needs to be informed by knowledge of the causes of this complex brain disorder. Emerging genetic, physiological, cognitive and systems-based imaging evidence of schizophrenia, in parallel with the emergence of clinically relevant preclinical translational assays, means that we are moving to a position of strength to advance drug discovery. Through these recent advances, scientists are now able to integrate this knowledge, placing us in a much stronger position to develop potential biomarkers for diagnosis and to tackle drug discovery from an informed translational perspective.

Major technological and analytical advances are now providing scientists with the opportunity to gain greater insight into the complex genetic architecture and the true nature of brain dysfunction at a systems level in schizophrenia. The integration of genetic information obtained from genome-wide association studies and other studies will provide new insight into the ways in which neural circuitry and downstream biological pathways are altered by candidate genes. This information paves the way for novel target identification and for the development of models with improved construct validity for drug development. Rather than relying on serendipitous strategies for target discovery, rational target design strategies can be implemented based on an enhanced understanding of how genetic pathways affect biological systems.

A recurring theme throughout this Review is that for a compound to be considered as a strong clinical candidate it should demonstrate efficacy in translationally relevant assays in models with high construct validity. Failures of previous strategies have arisen largely because of the persistence of using high-throughput, simple behavioural end points (which are of no translational value) in models that are of questionable relevance to the disease.

We now have a range of translational cognitive assays (for example, ASST and 5-CSRTT, with others being developed) that can be used for assessing compounds, as well as advanced imaging and electrophysiological methods that can inform on drug activity at the level of neural circuitry. We also have improved models based on genetic and environmental risk factors. To ensure optimal translation, these genetic models should have a strong molecular relationship with the genetic factors identified in patients with schizophrenia, and modelling of environmental risk factors should be appropriately timed during the developmental process.

Integration of genetic models and assays with classical pharmacological approaches offers great opportunities for drug discovery in schizophrenia and in neuropsychiatry as a whole. The preclinical validation of novel compounds must be aligned more closely with the clinical situation. This should include chronic drug administration and, for cognition-enhancing compounds that

are intended to be used as add-on treatments, preclinical validation should also be conducted during chronic antipsychotic drug treatment.

In conclusion, emerging genetic, cellular and brain imaging evidence is enabling the pieces of the schizophrenia jigsaw to be assembled. We now have the armoury, so the time is ripe to put aside the former ineffective approaches for schizophrenia drug discovery and replace them with high-quality integrated translational neuroscience programmes. Although this will often mean losing the seductively high throughput of simple assays in simple models, it is our hope that the advanced understanding of disease pathophysiology gained through these truly translational approaches will compensate, through the rational selection of empirically identified therapeutic targets.

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Competing interests statement
The authors declare no competing financial interests.

FURTHER INFORMATION

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