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Modeling resilience to schizophrenia in genetically modified mice: a novel approach to drug discovery

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Abstract

Complex psychiatric disorders, such as schizophrenia, arise from a combination of genetic, developmental, environmental and social factors. These vulnerabilities can be mitigated by adaptive factors in each of these domains engendering resilience. Modeling resilience in mice using transgenic approaches offers a direct path to intervention, as resilience mutations point directly to therapeutic targets. As prototypes for this approach, we discuss the three mouse models of schizophrenia resilience, all based on modulating glutamatergic synaptic transmission. This motivates the broader development of schizophrenia resilience mouse models independent of specific pathophysiological hypotheses as a strategy for drug discovery. Three guiding validation criteria are presented. A resilience-oriented approach should identify pharmacologically tractable targets and in turn offer new insights into pathophysiological mechanisms.

Keywords

antipsychotic; behavioral testing; D-amino acid oxidase; glutaminase; glycine transporter; latent inhibition; mouse model; neurodevelopmental disorder; prepulse inhibition; serine

Despite significant advances in the identification of risk genes for schizophrenia, no fundamentally new pharmacological treatments have emerged in several decades. Moreover, current treatments do not ameliorate cognitive symptoms, accounting for the significant morbidity associated with the disorder [1,2]. Although genetic factors play a major role in

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the etiology of schizophrenia, their contribution is multifaceted and complex, and no single gene has emerged as causative. It is also clear that nongenetic factors, such as epigenetic modulation [3–5] and neurodevelopmental insults [6], contribute significantly to the etiology of schizophrenia. Even precise knowledge of a single known risk gene with high impact does not translate directly to successful pharmacological treatment, as illustrated by the limited treatment options for Huntington's disease; linkage to chromosome 4 was reported in 1983 (over 25 years ago) and the huntingtin gene was identified in 1993 (over 15 years ago). Although there is growing insight into the pathological mechanisms in Huntington's disease [7], current treatments offer only limited symptom management [8,9]. With multiple genetic targets, having varying impacts and nongenetic etiological factors, the approach to schizophrenia must be inherently different. In this article, we argue that a systematic approach to identify genes conferring resilience, rather than vulnerability, is more readily translatable to pharmacotherapy acting at novel molecular targets.

Resilience is defined as positive adaptation and maintenance of competent functioning in the face of prolonged or severe stress [10]. Why, when exposed to certain insults, do some individuals develop pathological symptoms while others do not? Faced with hardship, resilient individuals demonstrate adaptive psychological and physiological coping responses or psychobiological allostasis [11]. The forces of vulnerability and resilience have environmental, genetic and social factors, as depicted in Figure 1. Forces of vulnerability can accelerate the progression of psychiatric disorders, such as schizophrenia, and are likely to be determined by an individual's genetic makeup and by environmental and social factors, such as early neurodevelopmental experience, psychological trauma or drug abuse. The forces of resilience, on the contrary, can preclude, reverse or slow the progression of the disease. Although resilience has been traditionally approached from a psychosocial perspective, focusing on environmental and social factors that protect from disease onset and progression, such as group therapy and the home environment [12], recent studies draw attention to genetic and epigenetic resilience factors [13].

In a seminal study on gene–environment interactions, Caspi *et al.* showed that individuals exposed to childhood stress who are homozygous for the long ('l') serotonin transporter (5-HTT) allele are less prone to depression than individuals with one or two copies of the short ('s') allele [14]. The 'l' allele may thus confer resilience to stressful life events that increase the risk for depression. Further studies in nonhuman primates similarly show that 5-HTT variation and early environment interact to influence social and affective behavior [15]. In a recent schizophrenia study, gray matter volume was shown to be associated with genetic variants in a polymorphism in the glycogen synthase kinase 3- β promoter [16]; carriers of the rs334558 C allele, which is associated with reduced activity of the enzyme, had higher gray matter volumes than homozygous carriers of the T allele; the authors hypothesize that “carrying the less active mutant C allele would protect the brain against neuropathological damage associated with schizophrenia” [16]. A recent study on mice revealed that a single-nucleotide polymorphism in the AMPA *GluR1* gene can determine vulnerability or resilience to stress [17]. These studies indicate that genetic factors, alone or in combination with environmental variables, play an important role in resilience to psychiatric disorders. The identification of genetic factors that enhance resilience is particularly important [18], as enhancing resilience may translate more directly into pharmacotherapy.

The genetic approach to psychiatric disorders has principally sought to identify genetic factors associated with disease, with the idea that this will shed light on disease mechanisms, suggest novel interventions and thereby advance the development of drugs [19]. Comparatively less effort has focused on identifying the genetic factors associated with resilience. While potentially related, genetic factors of vulnerability and resilience appear to be fundamentally different. Enhancing resilience in the setting of environmental stress does

not so much reverse stress-induced changes in gene activation, but rather activates new populations of genes [20]. Here, the authors focus on genetically modified mice as an approach to resilience-based drug discovery in schizophrenia. So far, potential targets for resilience approaches have been motivated by current insights into the etiology and pathophysiology of schizophrenia.

The etiology of schizophrenia: vulnerability & resilience to putative risk factors

Major etiological factors in schizophrenia include genetic variation, neurodevelopmental perturbations and alterations in dopamine, γ -amino butyric acid and glutamate synaptic transmission. It is now becoming very clear that there is no ultimate risk factor in schizophrenia driving illness progression or particular symptoms. Rather, an accumulation of etiological risk factors, some of which are broadly defined, determines vulnerability to the disorder.

The risk for schizophrenia is directly related to the genetic proximity of affected relatives; the concordance rates are 50 and 15% in monozygotic twins and dizygotic twins, respectively [21]. Overall, twin studies have shown that the heritability of schizophrenia approaches 80% [4]. Recent genome-wide association studies have identified specific risk loci and detected several novel rare copy-number variants. However, most associations are weak and account for only a small portion of the genetic risk [22]. Of the identified risk genes, the strongest linkage data point to 22q microdeletions [23], which involve multiple genes. Linkage studies in affected families also implicate several single genes such as *DISC1*, *COMT1*, reelin and neuregulin. Many recognized genetic alterations appear to have a convergent impact on glutamatergic synaptic transmission [24,25].

Human genetic studies have provided the basis for schizophrenia research in genetically modified mice [26–28]. However, no single gene or chromosomal region has emerged as having strong etiologic predictive value [29], leading to the notion that the ‘common disease, common variant’ hypothesis may not be useful in schizophrenia and may have to be replaced with a ‘common disease, multiple rare variants’ hypothesis, involving copy-number variations [30]. The possibility that there are genetic resilience factors, which are protective and counteract vulnerability conferred by risk genes or other etiological factors, adds further complexity. Genetic resilience factors could be inherited or generated *de novo*, providing a possible explanation for discordance in monozygotic twins, and more generally for cases where risk genes are present but symptoms are not. Notably, discordance in monozygotic twins raises the possibility that nongenetic etiological factors, for example, epigenetic [31] or neurodevelopmental [6] factors, are causally involved in schizophrenia.

Although significant shrinkage in several brain regions is seen in schizophrenia [5,32], neuropathological signs of cell injury such as gliosis are not evident [33]. Rather, subtle alterations in neuronal organization have been described, involving cortical interneurons [34–36]. Current thinking postulates that these impairments occur early in life. A large body of epidemiological research shows association of obstetric and perinatal complications with schizophrenia, including periventricular hemorrhages, hypoxia and ischemic injuries. There is also a robust collection of human studies [37], supported by rat and mouse studies, indicating that environmental insults during early-to-mid-gestation increase the risk of developing schizophrenia. In rats, *in utero* viral infection leads to schizophrenia-related behavioral phenotypes and changes in brain structure [38,39], and prenatal administration of methylazoxymethanol acetate induces a schizophrenia-like profile [40].

The onset of schizophrenia, however, is in adolescence or young adulthood. There is often a trigger that pushes a vulnerable individual to be diagnosed with schizophrenia. The critical role of stress in the onset or recrudescence of schizophrenia has been recognized for many years [41–43], with the hypothesis that this interaction involves activation of the hypothalamic–pituitary axis and increased dopamine release. There is a high correlation between substance abuse and schizophrenia. Substance abuse may be viewed as an attempt at self-medication, a premorbid precipitant or both [44]. Some studies have proposed that drug abuse could either cause short-term schizophrenia-like symptoms in healthy individuals or increase the likelihood of disease manifestation in vulnerable individuals. While early and late environmental factors undoubtedly play a role in schizophrenia vulnerability, it is also evident that there is great interpersonal variability in their impact. Prenatal influenza infections are common, as are drug use and stress; these factors, even when they co-occur in the same individual, do not necessarily lead to schizophrenia. Genetic predisposition may potentiate and enhance the effects of early or late environmental risk factors [45]. Similarly, resilience genes may protect certain individuals in the face of adverse environmental factors, and delay or prevent disease manifestation [13]. While multiple etiological pathways can give rise to schizophrenia, the pathophysiology – and also current treatment – involves altered neurotransmission.

Schizophrenia pathophysiology

The dopamine hypothesis of schizophrenia was formulated in the 1960s and posits that the symptoms of schizophrenia, particularly the positive symptom cluster, result from increased striatal extracellular dopamine levels [46]. This hypothesis is supported by clinical studies showing that amphetamine and other compounds that affect mesolimbic dopaminergic neurons induce positive symptoms, such as hallucinations and delusions, in healthy individuals, while D₂-receptor antagonists reduce positive symptoms in a dose-dependent manner [47]. Recent studies on mice indicate that elevated D₂ receptor levels in the striatum may engender cognitive symptoms [48,49], and another study suggests a more complex role for dopamine transmission in schizophrenia by showing that low dopamine levels in the prefrontal cortex are associated with negative and cognitive symptoms [50]. Despite its prominent role in schizophrenia treatment and research, the dopamine hypothesis has not furthered drug development beyond the long-established antipsychotic drugs; dopamine-based antipsychotic drugs, both typical and atypical, leave many patients with enduring symptoms, particularly negative and cognitive symptoms, and have debilitating side effects [46].

The glutamate hypothesis of schizophrenia initially focused on hypofunction of NMDA-type glutamate receptors, and later evolved to include increased glutamate release [51]. Enhancing NMDA receptor function and tempering glutamate release have become novel therapeutic targets. Glycine agonists, partial agonists and transport inhibitors that allosterically enhance NMDA receptor function have shown promise in countering schizophrenia symptoms [51,52]. Tempering excessive glutamate release via mGluR2/3 stimulation has been shown to have an efficacy comparable to that of current antipsychotic agents [53], and a Phase III clinical trial initiated during March 2011 is now ongoing. The pivotal role of altered glutamatergic transmission in schizophrenia is supported by the convergence of linkage to molecules involved in the development and functioning of glutamatergic synapses [24]. Research has turned to mouse models to elucidate the role of altered dopamine and glutamate synaptic transmission in schizophrenia.

Mouse models of schizophrenia vulnerability & resilience

There is growing recognition of the value of mouse models in the elucidation of neural mechanisms underlying vulnerability to psychiatric disorders, and in particular schizophrenia [29,35,54–57]. While translation from mouse models to therapeutic efficacy for human disorders has yielded mixed results, much of this reflects methodological limitations that are now being overcome; indeed, “the development of more sophisticated transgenic models, better humanized mice, and powerful small animal imaging platforms has shown that the mouse can be an effective gateway for translational research” [57].

Current mouse models of schizophrenia involve mutations in candidate genes [58], neurodevelopmental abnormalities [59] or mechanistically plausible alterations in neurotransmission [48,60]. A prime example is that NMDA receptor dysfunction in mice, both early in development [61] and throughout life [60], leads to schizophrenia-like abnormalities in adulthood. Such models variably demonstrate face, construct (etiologic) and predictive validity. However, animal models are inherently limited in recapitulating human neuropsychiatric disorders, and so are similarly limited in driving drug development [29,62]. Moreover, the transition from a mouse model of vulnerability to treatment often relies on the presumption that simply reversing the deficit induced in an animal model will prove to be therapeutic.

Future mouse models of resilience would circumvent this assumption by more directly testing the potential of a specific intervention as a treatment option. As detailed in the following section, currently published mouse models of resilience to schizophrenia have all been based on the glutamate hypothesis of schizophrenia. However, a promising possibility is that high-throughput studies, which are becoming increasingly feasible [63,64], could point towards mechanistically novel genes mediating resilience.

Criteria-based assessment of schizophrenia resilience in mice

Like models of disease vulnerability, mouse models of resilience should be subjected to the same requirements of construct, face and predictive validity. To assess resilience across the symptom domains of schizophrenia, particularly mechanistically novel models, three criteria should be considered: behavioral and neurochemical abnormalities induced by propsychotic manipulations should be attenuated, which may be genetic, neurodevelopmental or pharmacological; antipsychotic-like phenotypes should emerge at baseline, without prior drug treatment; and procognitive behavioral effects should manifest, particularly if the resilience model is pertinent to the treatment of cognitive symptoms. Aside from the desired antischizophrenia profile, it is crucial that mice show no gross deficits in motor, learning or affective behavior, pointing to a benign side-effect profile. These criteria are neither exhaustive nor conclusive, but should serve as a framework for further evaluation.

Criterion I: attenuation of propsychotic challenges

If a genetic alteration leads to a resilience phenotype, it should protect an individual from environmental stressors and from drug-induced neurochemical alterations. In mice, drugs that induce schizophrenia-like behaviors include the dopamine releaser amphetamine, which in humans leads to or exacerbates positive symptoms, and the NMDA receptor blocker phencyclidine [46] and its congeners ketamine and MK801, which induce both positive and negative symptoms. Both types of drugs enhance locomotor activity in rodents, and attenuation of this behavior is a key behavioral test for antipsychotic drug action [54,65]. At the neurochemical level, these propsychotic drugs induce enhanced dopamine release in the striatum [66] that is attenuated by anti psychotic drugs [67]. This first criterion, therefore, posits an attenuated motor response to the actions of amphetamine and NMDA receptor

antagonists, or attenuation of hyperactivity in a genetic model of schizophrenia, such as reduced *NR1* expression [60]. However, this criterion can be generalized to any behavior induced by amphetamine or by NMDA receptor blockade. For example, amphetamine and NMDA receptor antagonists induce deficits in latent inhibition (LI) and prepulse inhibition (PPI), and NR1 mutants display social interaction deficits. These disruptions are attenuated by antipsychotic drug pretreatment and should likewise be attenuated in mouse models of resilience. Although the examples given in the following sections pertain to the effects of propsychotic drugs, the first criterion can be generalized further, as mentioned above, to include alterations in behavior induced by environmental manipulations relevant to schizophrenia symptom onset, such as gestational immune activation or methylazoxymethanol acetate administration.

Criterion II: antipsychotic-like phenotype at baseline

While the first criterion of resilience screens for genetic alterations that reverse the effects of propsychotic manipulations, a genetic change that counteracts a change in a certain neurotransmitter system may not reflect a true resilience profile. Behavioral assays in rodents that allow testing for an antipsychotic-like drug action without prior drug administration include LI and PPI.

Latent inhibition

LI is a cross-species phenomenon, whereby the conditioned response to a stimulus that had been pre-exposed, or presented in the absence of reinforcement, is diminished in comparison to a nonreinforced stimulus. This phenomenon is commonly considered to index the ability to ignore stimuli that were previously irrelevant, and is disrupted in some patients with schizophrenia. Amphetamine was shown to disrupt LI in healthy individuals, and antipsychotic drugs such as chlorpromazine and haloperidol lead to enhanced LI, which can be demonstrated under conditions of no LI in the control condition. LI studies in the human population, either healthy or affected, have been conducted using several procedures, dependent variable measurements, and drug treatment regimens, often giving rise to conflicting results [68,69]. However, both amphetamine-induced disruption of LI and antipsychotic drug-induced enhancement of LI have been demonstrated by several groups, and these results have provided a basis for a study of LI in animals.

Dopamine releasers, such as amphetamine, induce an inability to ignore the irrelevant pre-exposed stimulus, (i.e., disrupted LI) in healthy humans and rodents [68]. NMDA antagonists such as MK801 produce the opposite effect in LI in rodents – namely, an abnormally enhanced or persistent LI [70–73]. While the effects of amphetamine mimic the positive symptoms of schizophrenia, MK801-induced enhancement of LI is thought to mimic perseverative behavior, part of the negative and cognitive symptom clusters [68].

In addition to reversing the effects of amphetamine and MK801 to restore normal LI, antipsychotic and procognitive drugs have an effect in the LI model at baseline. When given without prior administration of propsychotic compounds, both typical and atypical antipsychotic drugs lead to enhanced LI, which can be measured on the background of no LI in control animals. Some studies have also found enhanced LI following antipsychotic drug administration in healthy humans, although others reported disrupted LI or no effect, perhaps due to differences in methodologies or dependent variable measurement [69]. Notably, enhanced LI in animals could reflect either a propsychotic effect, similar to that of MK801, or an antipsychotic/procognitive profile, similar to that of clozapine or D-serine.

Interestingly, while clozapine induces enhanced LI when given on its own, it reverses MK801-induced LI enhancement. This distinction provides an important tool for

differentiating vulnerability and resilience with LI; a compound or manipulation that induces vulnerability to schizophrenia (such as MK801) will lead to enhanced LI that is reversed by clozapine, while a compound or manipulation that enhances resilience will lead to enhancement of LI that cannot be reversed, and may even be potentiated by clozapine.

Prepulse inhibition

PPI refers to the inhibition of a startle reflex that occurs when a strong acoustic stimulus is preceded by a barely detectable prepulse. PPI is disrupted in patients with schizophrenia, and is reduced in rodents that have undergone neurodevelopmental manipulations or received psychotomimetic drugs, including amphetamine, phencyclidine (PCP) and ketamine [74]. As in LI, clinically available and putative antipsychotic drugs reverse the disruption of PPI induced by psychotomimetic drugs [75–77], and enhance the PPI effect, especially in mouse strains, showing low levels of sensorimotor gating at baseline [78]. Genetic alterations leading to a resilience profile are, therefore, expected to attenuate the effects of amphetamine and NMDA receptor blockers on LI (Criterion I), but lead to antipsychotic-insensitive enhanced LI at baseline (Criterion II).

Criterion III: procognitive phenotypes

Enhancement of cognition represents a dimension of schizophrenia treatment that is both significant and independent of the treatment of other symptom domains [79]. Taking into consideration their expected cognitive abilities, almost all patients with schizophrenia show diminished cognitive performance, with poorer executive function, memory and processing speed (see [80] and references therein). Current antipsychotic medications, including atypical antipsychotics do not ameliorate cognitive symptoms [81], pointing to the pressing need to identify novel treatment strategies extending beyond control of positive symptoms for cognitive impairments in schizophrenia. Thus, enhanced cognitive performance in tests particularly relevant to cognitive symptoms in schizophrenia (see following section) is an important criterion, by itself or in combination with Criteria I and II, for mouse models of resilience. In concert with the importance of this criterion for identifying models of resilience, improved cognitive performance is also a prerequisite for the evaluation of novel pharmacological agents that aim at ameliorating cognitive dysfunction in schizophrenia [82].

Cognitive impairments in schizophrenia are studied in animals using tasks that tap into the cognitive domains impaired in schizophrenia. For example, executive function, which in humans can be measured using the Wisconsin Card Sorting Task, can be assessed in primates [83,84] and rodents [85,86] using attentional set shifting tasks. Learning and memory can also be measured using fear conditioning, delayed nonmatch to sample tasks, or radial arm maze tasks; such tests have recently been reviewed [87].

Genetic mouse models based on the glutamate hypothesis of schizophrenia

Resilience models can be based on neurodevelopmental or psycho-pharmacological manipulations; however, focusing on genetic manipulations engendering resilience may offer a more direct route to pharmacological treatment. In contrast to the many genetic mouse models of vulnerability to neuropsychiatric disorders, there are now a small, but increasing, number of genetic mouse models of resilience, which are listed for neuropsychiatric disorders other than schizophrenia in Table 1. Next, the authors review the three established schizophrenia resilience models. All were driven by the glutamate hypothesis of schizophrenia, and are listed in Table 2 – namely, the glycine transporter (GlyT1) deficiency, *Dao1*^{G181R} and *GLS1* het models. The models are considered according to the three criteria.

GlyT1-deficient mice

Genetically modified mice expressing reduced levels of the glycine transporter GlyT1 were generated to test the therapeutic potential of enhancing NMDA receptor function [88]. Glutamate-mediated transmission at the NMDA receptor is modulated by glycine, a coagonist, and so indirectly by GlyT1, which mediates the reuptake of glycine from the synaptic cleft, thereby modulating NMDA receptor function (see Figure 2; left column). Reductions in *GlyT1* expression should raise synaptic glycine levels and ameliorate NMDA receptor hypofunction. Several GlyT1 mouse mutants have been generated for the analysis of the physiological role of GlyT1, its impact on a wide spectrum of behavioral parameters and the potential of targeting GlyT1 as a pharmacotherapeutic approach.

While GlyT1-knockout (KO) mice die within 12 h of birth, heterozygous GlyT1 mice – with one functional GlyT1 allele – are viable, with a normal developmental trajectory despite having potentiated NMDA receptor function, as measured in hippocampal brain slice recordings [89,90]. Conditional mouse lines with regionally restricted KOs make it possible to bypass the lethality associated with full KOs and elucidate the neural basis for observed phenotypes, and thus the mechanism of resilience. To restrict the reduction in GlyT1 regionally, Singer *et al.* generated two novel mouse lines: one with a forebrain-specific neuronal GlyT1 reduction (GlyT1^{ΔFB-neuron}) by crossing α-CamKII Cre2834 mice with conditional GlyT1-KO mice (GlyT1^{tm1.2flox/flox}), and a second line using Emx1 cre to delete GlyT1 in the telencephalon (GlyT1^{ΔTelenceph}) [91]. Like GlyT1 hemizygous mice, GlyT1^{ΔFB-neuron} mice show enhanced NMDA receptor-mediated synaptic currents, whereas the NMDA receptor-mediated response in GlyT1^{ΔTelenceph} was unaltered [91].

In line with Criterion I, GlyT1-deficient mice demonstrate an attenuated response to the effects of psychotropic drugs, although this effect varies across mouse lines, manipulations and behavioral assays. As described above, amphetamine and NMDA receptor blockers, such as ketamine, PCP and MK801, induce locomotor activity in wild-type (WT) mice. This effect is attenuated in GlyT1 mutants: conditional KOs display reduced sensitivity to the motor-stimulating effects of NMDA receptor blockade and amphetamine [92] and constitutive GlyT1 hets show reduced amphetamine-induced hyperlocomotion [88]. The antipsychotic-like profile of GlyT1 mutants is less consistent when tested in other behavioral paradigms. Amphetamine and NMDA receptor blockers normally disrupt PPI, and these disruptions are reversed by antipsychotic drugs and by compounds that block the glycine transporter [88]. The resilience profile of GlyT1-deficient mouse lines in PPI, however, is incomplete: GlyT1 hets are resistant to the effects of amphetamine in PPI but show greater PPI disruption following MK801 administration. GlyT1^{ΔTelenceph} mice are resistant to the effects of NMDA receptor blockade in the PPI model, but GlyT1^{ΔFB-neuron} mice are not. While these differences could be due to interactions between different neurotransmitter systems in PPI, or to different patterns of interference with PPI circuitry in the different GlyT1 mouse lines, testing Criterion I for GlyT1 mutants will require further study.

Regarding Criterion II, there is no enhancement of PPI in mice with a constitutive disruption of GlyT1 function [90] or in GlyT1^{ΔTelenceph} mice [93]. Curiously, mice with a forebrain-specific deletion GlyT1^{ΔFB-neuron} show disrupted PPI [93]. These findings indicate that GlyT1 blockade in different brain regions may lead to mechanistically different effects on neurotransmitter interactions, and thus produce different behavioral effects. The lack of effect in GlyT1 hets stands in contrast to the enhanced PPI effect observed following pharmacological blockade of glycine transporters [94]. This contradiction may be due to strain differences [78], acute versus long-term reduction in GlyT1 in pharmacological and genetic models, respectively, or a simple dose–response effect; for example, Lipina *et al.* showed that at high doses, the glycine transport blocker ALX5407 acts similarly to an

NMDA receptor blocker and disrupts PPI [72]. The basis of these contradictory findings needs to be addressed.

GlyT1^{Telenceph} mice show unaltered LI [91,95], while forebrain-specific GlyT1 KO mice display antipsychotic drug-like LI potentiation at baseline [92], indicating a possible resilience profile in line with Criterion II, and with the procognitive profile of this mouse (see below). However, since LI potentiation could also represent an MK801-like effect (consistent perhaps with the sensitized response of GlyT1 hets to MK801 in PPI), it would be interesting to examine the responsiveness of LI enhancement in GlyT1^{ΔFB-neuron} mice to clozapine treatment.

Addressing Criterion III, GlyT1 deficiency, particularly in forebrain neurons, induces enhanced performance in several cognitive tests. GlyT1^{ΔFB-neuron} mice outperform WT mice in tests of novel object recognition, associative learning and behavioral flexibility. The interpretation of these results was that “GlyT1^{ΔFB-neuron} mice might be less susceptible to proactive interference and therefore accorded with more flexible and adaptive behavioral control” [95]. Additional cognitive tests need to be carried out to obtain a fuller picture of the advantages conferred by GlyT deletion on cognitive performance.

An integrated analysis of behavioral and pharmacological data collected in GlyT1-deficient mice reveals that the three criteria of resilience are at least partially fulfilled; however, some questions remain to be answered and there are some inconsistencies that remain to be resolved (Table 2). GlyT1-deficient mice display an attenuated or delayed response to propsychotic drugs, show an antipsychotic-like profile in the LI model and outperform control mice in measures of cognitive function. The schizophrenia resilience profile of GlyT1 genetic models is further supported by pharmacological studies with a number of GlyT1 inhibitors, which have demonstrated therapeutic potential in preclinical and clinical studies [89,94,96–100]. Indeed, RG1678, a selective GlyT1 transport inhibitor, has shown promise in Phase II clinical trials [101], and is currently in Phase III trials.

DAO1 mutant mice

A second schizophrenia resilience model, similarly focusing on the NMDA receptor, utilizes mice with a mutation in D-amino-oxidase (*DAO*) [102,103]. DAO is an enzyme responsible for the catabolism of D-serine, an indirect NMDA receptor agonist that binds to the glycine coagonist site on the NR1 subunit (Figure 2; middle column). While both glycine and D-serine bind to the coagonist site and potentiate NMDA receptor function, D-serine is probably the endogenous ligand, and its distribution in the brain parallels that of the NMDA receptor [104]. An *in vivo* functional MRI (fMRI) study measuring cerebral blood volume (CBV) found enhanced hippocampal activation following D-serine administration in rats [105], and several human studies point to the importance of the D-serine pathway in schizophrenia [104]. Mice with a spontaneous G18R point mutation in the *DAO* gene (DAO1^{G18R} mice) have a single base pair substitution that renders the DAO enzyme inactive [102,106]. As would be expected, elevated levels of D-serine and enhanced NMDA receptor function were observed in these mice [107], pointing to their possible relevance as a model of resilience.

Using a novel approach for testing the therapeutic potential of DAO inhibition [108], DAO1^{G18R} mice were crossed with the previously mentioned Grin1^{D481N} mice, which have reduced NMDA receptor function and display behavioral abnormalities relevant to schizophrenia pathology [60]. In line with Criterion I, the DAO1^{G18R}–Grin1^{D481N} double-mutant mice show a reversal of some of the schizophrenia-associated cognitive deficits conferred by the *NR1* mutation, including LI abnormalities and elevated startle reactivity [108]. Moreover, the double mutants display a reversal of the social approach and

spatial memory retention deficits seen in the *Grin1D481N* mutants. In addition, in line with Criterion I, mice carrying a mutation in the *DAO1* gene show reduced locomotor stimulation in response to the administration of psychotomimetic drugs such as MK801 [109] and methamphetamine [103], while displaying normal motor, social and cognitive behavior at baseline. Taken together, these findings indicate that *DAO1*^{G181R} mice are resilient to the effects of genetic or pharmacological manipulations that induce schizophrenia-like phenotypes.

Clozapine-like potentiation of LI, Criterion II, was not seen in *DAO1*^{G181R} mice [108], although as mentioned above, the *DAO1 G181R* mutation was capable of reversing the abnormally persistent LI effect found in *Grin1D481N* mutants and did not induce LI disruption on its own. The potentiation of LI has long been viewed as a signature mark of antipsychotic drug action; pharmacological administration of D-serine and related compounds leads to potentiation of LI (see more detailed account above [71,72]). As for the GlyT1 hets, the inability of the *DAO1 G181R* mutation, which increases D-serine levels and NMDA receptor function, to potentiate LI may be to do with the chronicity of the mutation as compared with acute pharmacological actions. In a recent study, *DAO1*^{G181R} mice displayed enhanced PPI [110], which as described above has also been used as a screening test for antipsychotic action. However, this finding contrasts with previous data, where no alterations in baseline PPI were found in mice lacking DAO [111]. Differences between the two studies may be due to different parameters in the PPI assay [110]. In line with Criterion III, *DAO1*^{G181R} mice display improved memory for novel spatial locations, and accelerated extinction of spatial learning [112], interpreted by us as enhanced adaptive learning in response to changing conditions. *DAO1*^{G181R} mice also displayed increased escape latency in the Barnes maze [110], and superior performance in the Morris Water Maze task, along with enhanced LTP [113].

The *DAO1*^{G181R} mouse model holds promise for drug development, as the model meets most, if not all, of the resilience criteria. Success in clinical trials has been reported with D-serine or related compounds as secondary or adjunctive pharmacotherapies for schizophrenia [114–116], although the data are not consistent even here [117], and the metabolism of high doses of D-serine by DAO can produce cytotoxic metabolites [118,119]. It should be noted that treatment with D-serine is not analogous to directly inhibiting DAO function. Nonetheless, high-throughput screening in a cell-based DAO assay has yielded a few promising drug candidates with high specificity [120], and DAO inhibitors have shown promise in preclinical trials [121]. Interestingly, chlorpromazine was shown to block DAO activity over 50 years ago [122], which was confirmed in a recent study [123].

GLS1 het mice

The propsychotic effects of NMDA receptor antagonists suggest that schizophrenia is a state of deficient glutamate signaling. However, further studies have revealed that NMDA receptor antagonists, such as PCP and ketamine, paradoxically increase glutamate release [124–126], and that blockade of excessive glutamate release normalizes a schizophrenia-like phenotype in rats [127]. Manipulations that target the glutamate transporter and putatively increase glutamate concentrations lead to a schizophrenia-like phenotype in mice [128]. A recent study showed that optogenetically induced activation of excitatory transmission, presumably by enhancing glutamate release from primary cortical neurons in the mouse medial prefrontal cortex, produces schizophrenia-like social interaction deficits [129]. In humans, elevated levels of glutamate and glutamatergic markers have been found in first-episode drug-naïve patients with schizophrenia [130] and in schizophrenia-prone individuals [131]. Furthermore, clinical trials with drugs that decrease glutamate transmission via presynaptic mechanisms, such as anticonvulsants [132] and metabotropic mGluR2/3 agonists [53], have yielded promising results.

Because of the complexity and dynamic nature of the glutamate system, as well as of the disease itself, it has been difficult to resolve whether a global decrease in glutamatergic transmission, independent of changes in specific glutamate receptor types, would in fact lead to schizophrenia-like psychopathology. Gaisler-Salomon *et al.* asked whether a subtle activity-dependent presynaptic reduction in glutamate release, induced by a heterozygous deletion of glutaminase (gene: *GLS1*), would engender a schizophrenia-like phenotype in mice (see Figure 2; right column) [133]. The idea was that if NMDA receptor hypo-function is necessary and sufficient for inducing schizophrenia-like phenotypes, then *GLS1* deficiency should model schizophrenia; while if increased glutamate release is causally related to schizophrenia symptoms, then *GLS1* deficiency should model schizophrenia resilience.

Although *GLS1* KO mice die shortly after birth, apparently as a result of altered glutamatergic transmission in brainstem respiratory nuclei [134], *GLS1* hets, with one functional *GLS1* allele, are ostensibly normal. Arguably, heterozygous mice model drug action better as they mimic the partial blockade achieved by most psychotropics. Consistent with Criterion I, *GLS1* hets respond less to amphetamine, show reduced amphetamine-induced locomotion and reduced striatal dopamine release. They also show a diminished response to ketamine; *in vivo* fMRI imaging shows that unlike their WT littermates, *GLS1* hets display no increase in frontal cortex activity following the administration of this NMDA receptor blocker, commonly shown to enhance pre-frontal cortex activity in patients with schizophrenia [135]. Thus, *GLS1* hets are resilient to some of the pathological processes induced by dopaminergic and glutamatergic propsychotic drugs. At baseline, *GLS1* hets show normal behavior on a range of tests, with the exception of context learning, which is mildly impaired. This effect could be interpreted as a reduced tendency to form questionably relevant associations between neutral contextual cues and relevant stimuli, indicating a tempered predisposition to delusional processes. In line with Criterion II, *GLS1* hets also demonstrate enhanced LI at baseline which, unlike MK801-induced abnormally enhanced LI, was not reversed by clozapine pretreatment.

Another baseline phenotype of *GLS1* hets was revealed by resting state *in vivo* fMRI. While *GLS1* expression is reduced throughout the hippocampus and cortex of *GLS1* hets [136], functional brain imaging measuring relative CBV showed focal reduction in the hippocampus, particularly in the CA1 subregion [133]. At the same time, a human imaging study measuring CBV in patients with schizophrenia and a group of prodromal subjects pointed to a focal hyperactivity in the hippocampus, particularly in the CA1 subregion [137]. The imaging phenotype of the *GLS1* hets is the inverse of the phenotype seen in patients, suggesting that a reduction in glutaminase activity would attenuate pathological hyperactivity in CA1 selectively.

Regarding Criterion III, the cognitive performance of *GLS1* hets is barely affected, as the mice show no alterations in spatial memory, working memory or novel object recognition. The mice show an enhanced trace fear conditioning [Hazan L, Gaisler-Salomon L, Unpublished Data], suggestive of modest procognitive phenotype; however, a more comprehensive evaluation of the mice, with a particular emphasis on cognitive function, has yet to be performed. Possibly greater inhibition of glutaminase activity or of glutamate release would be required for procognitive effects. In *GLS1* hets, glutaminase activity is reduced by approximately 50%; however, glutamate levels are diminished by only approximately 15% [133]. Dose–response studies with future glutaminase inhibitors could determine whether greater blockade of glutaminase function would lead to superior cognitive performance. It is also possible that enhancement of cognitive function in *GLS1* hets, and in other models of resilience, may only be observed in a model of deteriorated

performance. Thus, it would be interesting to test the effects of GLS1 reduction in neurodevelopmental models of schizophrenia.

Overall, a reduction in GLS1 function engenders endophenotypic changes suggestive of resilience to schizophrenia. Moreover, the global GLS1 deficiency seen in GLS1 hets mainly has its impact in the hippocampus and cortex in young adulthood [136], arguing that systemic GLS1 inhibitors would have an impact similar to the GLS1 het mutation and would therefore be suitable for drug development. However, no CNS-active inhibitors of glutaminase are currently available.

Nonglutamatergic mouse models of resilience

Although the three resilience models outlined focus on glutamatergic synaptic transmission, other mouse models with a genetic modification affecting other neurotransmitter systems could be evaluated using the proposed criteria. For example, mice heterozygous for a mutation in the Netrin1 receptor, also known as ‘deleted in colon cancer’ (*DCC*), are resistant to the behavioral effects of amphetamine [138–140]. However, the developmental nature of the effect of the *DCC* mutation and its critical role in establishing the functionality of the mesocortical dopamine topography [139,141] makes it unlikely that inhibition in adulthood would be beneficial. Other prime candidates for the development of schizophrenia resilience models include heterozygous mice for genes involved in dopamine D₂ receptor postsynaptic signaling [142]. The glycogen synthase kinase 3- β het [143], the β -arrestin 2 KO [144] and the DARP32 KO [145] mouse models show decreased sensitivity to amphetamine and model components of antipsychotic drug action [146], but these models have not been explored as resilience models.

Expert commentary

Animal models of disease or disease vulnerability aim to go from disease gene to pathogenic mechanism, to rational intervention. However, the focus on the underlying etiology is at a considerable distance from therapeutic intervention. For neurodevelopmental disorders, such as schizophrenia, treatments aiming to reverse pathological processes starting in early life are unlikely to be effective in adulthood when the disorder is diagnosed. Rather, the authors argue that therapeutic approaches must focus on pathophysiology. The three published schizophrenia resilience mouse models have been reviewed, all of which were driven by the glutamate hypothesis. The models highlight how focusing on resilience, rather than vulnerability, offers a novel path for drug development in schizophrenia. While the GlyT1 and DAO models grew out of existing literature in schizophrenia, and were examined in parallel with pharmacological studies of compounds with the same or similar effects on glutamate synaptic transmission, the GLS1 het model was different, in that it was not clear from the outset whether GLS1 het mice would model vulnerability or resilience to schizophrenia. There is also no literature on pharmacological modification of glutaminase (as there are no known CNS inhibitors), which would have indicated whether glutaminase deficiency would model risk or resilience, or be at all relevant to schizophrenia. In that regard, the investigation of the phenotype of the GLS1 het mouse was unbiased to disease or resilience. Animal models of resilience offer particular utility for targets for which there are no known pharmacological modulators. When such models are investigated, the approach is indeed agnostic, and their value may be determined using the proposed resilience criteria.

Resilience targets can be identified based on current and future pathophysiological hypotheses, as illustrated in the three resilience models discussed. Studying genetically modified mice that fulfill the three criteria of resilience (Table 2) offers a systematic method for evaluating novel targets for symptom reduction and the possible delay, attenuation or prevention of disease onset, especially now that mouse lines with targeted

mutations across much of the genome are becoming widely available [63,64]. It should be stressed that the proposed criteria are not rigid; rather, they should serve as a starting point for refining criteria that best identify resilience to schizophrenia in animal models.

Finding a therapy through a working animal resilience model can be seen as a screening strategy to foster controlled serendipity. Broader, but focused, screening may involve mice that demonstrate one or more of the three resilience criteria, which will benefit from the systematic cataloguing of the behavior of genetically modified mice [147]. Genes regulating postreceptor signaling pathways may be identified by genetic pathway analyses as potential resilience targets. A further strategy might involve whole-genome scans in monozygotic twins discordant for schizophrenia, looking for genetic alterations in the unaffected twin that might be associated with resilience. So far, this has been performed looking only for genetic changes associated with the disorder [148], not with resilience.

No mouse model is perfect, as illustrated in Table 2. For example, GLS1 hets meet the first criterion of resilience, as they are less sensitive to amphetamine-induced locomotor activation, but not the third criterion, as they also show reduced contextual learning. It remains to be determined whether the reduced capacity of GLS1 hets to acquire or express contextual information is part of their resilient profile or is a side effect. This, and other examples of conflicting evidence in resilience models, highlight the likely possibility that resilience – just like vulnerability – cannot be fully recapitulated in mice. Rather, particular symptoms or symptom clusters can be modeled. Nonetheless, such advances may well identify novel targets for pharmacotherapies, or possibly secondary or adjunctive pharmacotherapies that together with established antipsychotics might achieve better outcomes.

The current schizophrenia resilience mouse models involve constitutive mutations. As the mutations are operative over the lifespan of the mice, one cannot be sure that the impact is principally in development, maturity or both. There are precedents for constitutive mutations affecting emotional and cognitive behavior that show phenotypes opposite to the corresponding pharmacological effects in adulthood [149,150], while others have the same effect as the pharmacological treatment [151]. This potential confound can be addressed using a genetic pharmacotherapy approach in which an inducible global deleter mouse is crossed with a mouse bearing a conditional version of the targeted allele to enable induction of the knockdown or KO in adulthood [152].

In summary, resilience can be modeled in the same way as vulnerability, and should be evaluated using systematic and uniform criteria. The resilience approach has the distinct merit of connecting directly to therapeutic intervention. Potential drug treatments stemming from the resilience models discussed, or related to them, are in different stages of development. Finally, as our current pharmacotherapies have informed our understanding of the underlying pathophysiology, identifying new treatment targets will likely offer new mechanistic insights, and *vice versa*.

Five-year view

Traditional pharmaceutical discovery approaches for CNS disorders have not ‘reaped significant benefits’ in the past two decades, and are now being discontinued in favor of programs that focus on genetic vulnerability (see page 161 of reference [153]). While genetic studies will move closer to identifying schizophrenia vulnerability genes and provide greater insight into pathogenesis, these advances will be slower in shedding light upon pathophysiology, as has been the case for genes already identified in linkage studies. Developing treatments to counter pathophysiology will require insights beyond reversing pathogenesis. As models of resilience inevitably reflect interpersonal variability, this

approach is likely to provide valuable information for personalized medicine, where treatment is customized to individual patients. New mouse models of resilience in schizophrenia research may emerge as a result of a focused effort to understand pathophysiology better, or as a result of directed phenotypic screening of genetically modified mice. Resilience models offer a novel and more direct approach to drug discovery for schizophrenia and neuropsychiatric disorders that should move the field forward from ‘me-too’ drugs to novel treatments.

References

Papers of special note have been highlighted as:

• of interest

•• of considerable interest

1. Insel TR. Rethinking schizophrenia. *Nature*. 2010; 468(7321):187–193. [PubMed: 21068826]
2. Karam CS, Ballon JS, Bivens NM, et al. Signaling pathways in schizophrenia: emerging targets and therapeutic strategies. *Trends Pharmacol Sci*. 2010; 31(8):381–390. [PubMed: 20579747]
3. Lupski JR. Schizophrenia: incriminating genomic evidence. *Nature*. 2008; 455(7210):178–179. [PubMed: 18784712]
4. Owen MJ, Craddock N, O'Donovan MC. Suggestion of roles for both common and rare risk variants in genome-wide studies of schizophrenia. *Arch Gen Psychiatr*. 2010; 67(7):667–673. [PubMed: 20603448]
5. Meyer-Lindenberg A. From maps to mechanisms through neuroimaging of schizophrenia. *Nature*. 2010; 468(7321):194–202. [PubMed: 21068827]
6. Fatemi SH, Folsom TD. The neurodevelopmental hypothesis of schizophrenia, revisited. *Schizophr Bull*. 2009; 35(3):528–548. [PubMed: 19223657]
7. Oliveira JM. Nature and cause of mitochondrial dysfunction in Huntington's disease: focusing on huntingtin and the striatum. *J Neurochem*. 2010; 114(1):1–12. [PubMed: 20403078]
8. Bossy-Wetzel E, Petrilli A, Knott AB. Mutant huntingtin and mitochondrial dysfunction. *Trends Neurosci*. 2008; 31(12):609–616. [PubMed: 18951640]
9. Rosenstock TR, Duarte AI, Rego AC. Mitochondrial-associated metabolic changes and neurodegeneration in Huntington's disease – from clinical features to the bench. *Curr Drug Targets*. 2010; 11(10):1218–1236. [PubMed: 20840066]
10. Lutha SS, Cicchetti D. The construct of resilience: implications for interventions and social policies. *Dev Psychopathol*. 2000; 12(4):857–885. [PubMed: 11202047]
- 11••. Feder A, Nestler EJ, Charney DS. Psychobiology and molecular genetics of resilience. *Nat Rev Neurosci*. 2009; 10(6):446–457. Cogent review of the resilience perspective. [PubMed: 19455174]
12. Cicchetti D, Rogosch FA. Adaptive coping under conditions of extreme stress: multilevel influences on the determinants of resilience in maltreated children. *New Dir Child Adolesc Dev*. 2009; 2009(124):47–59. [PubMed: 19536787]
13. Rutter M, Moffitt TE, Caspi A. Gene–environment interplay and psychopathology: multiple varieties but real effects. *J Child Psychol Psychiatr*. 2006; 47(3–4):226–261.
- 14••. Caspi A, Sugden K, Moffitt TE, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science*. 2003; 301(5631):386–389. Epidemiological study showing that a functional polymorphism in the promoter region of the serotonin transporter (5-HTT) gene can determine an individual's susceptibility or resilience to depression as a function of environmental insults. [PubMed: 12869766]
15. Suomi SJ. Risk, resilience, and gene–environment interplay in primates. *J Can Acad Child Adolesc Psychiatr*. 2011; 20(4):289–297.

16. Benedetti F, Poletti S, Radaelli D, et al. Temporal lobe grey matter volume in schizophrenia is associated with a genetic polymorphism influencing glycogen synthase kinase 3- β activity. *Genes Brain Behav.* 2010; 9(4):365–371. [PubMed: 20113358]
17. Schmidt MV, Trümbach D, Weber P, et al. Individual stress vulnerability is predicted by short-term memory and AMPA receptor subunit ratio in the hippocampus. *J Neurosci.* 2010; 30(50):16949–16958. [PubMed: 21159965]
18. Liberzon I, Knox D. Expanding our understanding of neurobiological mechanisms of resilience by using animal models. *Neuropsychopharmacology.* 2012; 37(2):317–318. [PubMed: 22157946]
19. Rasetti R, Weinberger DR. Intermediate phenotypes in psychiatric disorders. *Curr Opin Genet Dev.* 2011; 21(3):340–348. [PubMed: 21376566]
20. Robison AJ, Nestler EJ. Transcriptional and epigenetic mechanisms of addiction. *Nat Rev Neurosci.* 2011; 12(11):623–637. [PubMed: 21989194]
21. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatr.* 2003; 160(4):636–645. [PubMed: 12668349]
22. Gershon ES, Alliey-Rodriguez N, Liu C. After GWAS: searching for genetic risk for schizophrenia and bipolar disorder. *Am J Psychiatr.* 2011; 168(3):253–256. [PubMed: 21285144]
23. Karayiorgou M, Simon TJ, Gogos JA. 22q11.2 microdeletions: linking DNA structural variation to brain dysfunction and schizophrenia. *Nat Rev Neurosci.* 2010; 11(6):402–416. [PubMed: 20485365]
24. Harrison PJ, Weinberger DR. Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. *Mol Psychiatr.* 2005; 10(1):40–68. image 5.
25. Carter CJ. Schizophrenia susceptibility genes converge on interlinked pathways related to glutamatergic transmission and long-term potentiation, oxidative stress and oligodendrocyte viability. *Schizophr Res.* 2006; 86(1–3):1–14. [PubMed: 16842972]
26. Lee FH, Fadel MP, Preston-Maher K, et al. Disc1 point mutations in mice affect development of the cerebral cortex. *J Neurosci.* 2011; 31(9):3197–3206. [PubMed: 21368031]
27. Sigurdsson T, Stark KL, Karayiorgou M, Gogos JA, Gordon JA. Impaired hippocampal-prefrontal synchrony in a genetic mouse model of schizophrenia. *Nature.* 2010; 464(7289):763–767. [PubMed: 20360742]
28. Kato T, Kasai A, Mizuno M, et al. Phenotypic characterization of transgenic mice overexpressing neuregulin-1. *PLoS ONE.* 2010; 5(12):e14185. [PubMed: 21151609]
29. Nestler EJ, Hyman SE. Animal models of neuropsychiatric disorders. *Nat Neurosci.* 2010; 13(10):1161–1169. An important review of the current state of animal models of mental illness, focusing on schizophrenia, depression and bipolar disorder, and emphasizing the importance of explicit guidelines in evaluating animal models of psychiatric conditions. [PubMed: 20877280]
30. Schwab SG, Wildenauer DB. Update on key previously proposed candidate genes for schizophrenia. *Curr Opin Psychiatr.* 2009; 22(2):147–153.
31. Petronis A, Gottesman II, Kan P, et al. Monozygotic twins exhibit numerous epigenetic differences: clues to twin discordance? *Schizophr Bull.* 2003; 29(1):169–178. [PubMed: 12908672]
32. Honea R, Crow TJ, Passingham D, Mackay CE. Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. *Am J Psychiatr.* 2005; 162(12):2233–2245. [PubMed: 16330585]
33. Meyer-Lindenberg A. Neuroimaging and the question of neurodegeneration in schizophrenia. *Prog Neurobiol.* 2011; 95(4):514–516. [PubMed: 21801804]
34. Lewis DA, Hashimoto T. Deciphering the disease process of schizophrenia: the contribution of cortical GABA neurons. *Int Rev Neurobiol.* 2007; 78:109–131. [PubMed: 17349859]
35. Jaaro-Peled H, Ayhan Y, Pletnikov MV, Sawa A. Review of pathological hallmarks of schizophrenia: comparison of genetic models with patients and nongenetic models. *Schizophr Bull.* 2010; 36(2):301–313. [PubMed: 19903746]
36. Volk DW, Lewis DA. Prefrontal cortical circuits in schizophrenia. *Curr Top Behav Neurosci.* 2010; 4:485–508. [PubMed: 21312410]
37. Brown, AS.; Patterson, PH. *The Origins of Schizophrenia.* Columbia University Press; NY, USA: 2012.

38. Piontkewitz Y, Assaf Y, Weiner I. Clozapine administration in adolescence prevents postpubertal emergence of brain structural pathology in an animal model of schizophrenia. *Biol Psychiatry*. 2009; 66(11):1038–1046.
39. Piontkewitz Y, Arad M, Weiner I. Abnormal trajectories of neurodevelopment and behavior following *in utero* insult in the rat. *Biol Psychiatry*. 2011; 70(9):842–851.
40. Lodge DJ, Grace AA. Hippocampal dysfunction and disruption of dopamine system regulation in an animal model of schizophrenia. *Neurotox Res*. 2008; 14(2–3):97–104. [PubMed: 19073417]
41. Walker EF, Diforio D. Schizophrenia: a neural diathesis-stress model. *Psychol Rev*. 1997; 104(4): 667–685. [PubMed: 9337628]
42. Jones SR, Fernyhough C. A new look at the neural diathesis–stress model of schizophrenia: the primacy of social-evaluative and uncontrollable situations. *Schizophr Bull*. 2007; 33(5):1171–1177. [PubMed: 17105966]
43. van Os J, Kenis G, Rutten BP. The environment and schizophrenia. *Nature*. 2010; 468(7321):203–212. [PubMed: 21068828]
44. Potvin S, Stip E, Roy J. Schizophrenia and addiction: an evaluation of the self-medication hypothesis. *L'Encéphale*. 2003; 29(3):193–203.
45. Bayer TA, Falkai P, Maier W. Genetic and non-genetic vulnerability factors in schizophrenia: the basis of the 'two hit hypothesis'. *J Psychiatr Res*. 1999; 33(6):543–548. [PubMed: 10628531]
- 46•. Lieberman JA, Bymaster FP, Meltzer HY, et al. Antipsychotic drugs: comparison in animal models of efficacy, neurotransmitter regulation, and neuroprotection. *Pharmacol Rev*. 2008; 60(3):358–403. Current status of pharmacotherapies for schizophrenia. [PubMed: 18922967]
47. Abi-Dargham A, van de Giessen E, Slifstein M, Kegeles LS, Laruelle M. Baseline and amphetamine-stimulated dopamine activity are related in drug-naïve schizophrenic subjects. *Biol Psychiatry*. 2009; 65(12):1091–1093.
48. Kellendonk C, Simpson EH, Polan HJ, et al. Transient and selective overexpression of dopamine D₂ receptors in the striatum causes persistent abnormalities in prefrontal cortex functioning. *Neuron*. 2006; 49(4):603–615. [PubMed: 16476668]
49. Simpson EH, Kellendonk C, Kandel E. A possible role for the striatum in the pathogenesis of the cognitive symptoms of schizophrenia. *Neuron*. 2010; 65(5):585–596. [PubMed: 20223196]
50. Guillin O, Abi-Dargham A, Laruelle M. Neurobiology of dopamine in schizophrenia. *Int Rev Neurobiol*. 2007; 78:1–39. [PubMed: 17349856]
- 51••. Moghaddam B, Javitt D. From revolution to evolution: the glutamate hypothesis of schizophrenia and its implication for treatment. *Neuropsychopharmacology*. 2012; 37(1):4–15. An important review of the current understanding of the complex role played by glutamate in schizophrenia. [PubMed: 21956446]
52. Shim G, Kang DH, Chung YS, Yoo SY, Shin NY, Kwon JS. Social functioning deficits in young people at risk for schizophrenia. *Aust NZ J Psychiatr*. 2008; 42(8):678–685.
53. Patil ST, Zhang L, Martenyi F, et al. Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: a randomized Phase 2 clinical trial. *Nat Med*. 2007; 13(9):1102–1107. [PubMed: 17767166]
54. Moore H. The role of rodent models in the discovery of new treatments for schizophrenia: updating our strategy. *Schizophr Bull*. 2010; 36(6):1066–1072. [PubMed: 20870929]
55. Geyer MA. Developing translational animal models for symptoms of schizophrenia or bipolar mania. *Neurotox Res*. 2008; 14(1):71–78. [PubMed: 18790726]
56. Papaleo F, Lipska BK, Weinberger DR. Mouse models of genetic effects on cognition: relevance to schizophrenia. *Neuropharmacology*. 2012; 62(3):1204–1220. [PubMed: 21557953]
- 57•. Dow LE, Lowe SW. Life in the fast lane: mammalian disease models in the genomics era. *Cell*. 2012; 148(6):1099–1109. A review of the contribution genetically engineered mice have made to the understanding of human disease states. [PubMed: 22424222]
- 58••. Arguello PA, Markx S, Gogos JA, Karayiorgou M. Development of animal models for schizophrenia. *Dis Model Mech*. 2010; 3(1–2):22–26. Cogent review of mouse models of schizophrenia. [PubMed: 20075378]

59. Bitanirwe BK, Lim MP, Kelley JF, Kaneko T, Woo TU. Glutamatergic deficits and parvalbumin-containing inhibitory neurons in the prefrontal cortex in schizophrenia. *BMC Psychiatr.* 2009; 9:71.
60. Mohn AR, Gainetdinov RR, Caron MG, Koller BH. Mice with reduced NMDA receptor expression display behaviors related to schizophrenia. *Cell.* 1999; 98(4):427–436. [PubMed: 10481908]
61. Belforte JE, Zsiros V, Sklar ER, et al. Postnatal NMDA receptor ablation in corticolimbic interneurons confers schizophrenia-like phenotypes. *Nat Neurosci.* 2010; 13(1):76–83. [PubMed: 19915563]
62. Enna SJ, Williams M. Challenges in the search for drugs to treat central nervous system disorders. *J Pharmacol Exp Ther.* 2009; 329(2):404–411. [PubMed: 19182069]
63. Skarnes WC, Rosen B, West AP, et al. A conditional knockout resource for the genome-wide study of mouse gene function. *Nature.* 2011; 474(7351):337–342. [PubMed: 21677750]
64. Dow LE, Premsrirut PK, Zuber J, et al. A pipeline for the generation of shRNA transgenic mice. *Nat Protoc.* 2012; 7(2):374–393. [PubMed: 22301776]
65. Arguello PA, Gogos JA. Modeling madness in mice: one piece at a time. *Neuron.* 2006; 52(1):179–196. [PubMed: 17015235]
66. Kegeles LS, Abi-Dargham A, Frankle WG, et al. Increased synaptic dopamine function in associative regions of the striatum in schizophrenia. *Arch Gen Psychiatr.* 2010; 67(3):231–239. [PubMed: 20194823]
67. Nordström AL, Farde L, Wiesel FA, et al. Central D₂-dopamine receptor occupancy in relation to antipsychotic drug effects: a double-blind PET study of schizophrenic patients. *Biol Psychiatr.* 1993; 33(4):227–235.
68. Weiner I, Arad M. Using the pharmacology of latent inhibition to model domains of pathology in schizophrenia and their treatment. *Behav Brain Res.* 2009; 204(2):369–386. [PubMed: 19433114]
69. Schmidt-Hansen M, Le Pelley M. The positive symptoms of acute schizophrenia and latent inhibition in humans and animals: underpinned by the same process(es)? *Cogn Neuropsychiatr.* 2012 (Epub ahead of print). 10.1080/13546805.2012.667202
70. Gaisler-Salomon I, Weiner I. Systemic administration of MK-801 produces an abnormally persistent latent inhibition which is reversed by clozapine but not haloperidol. *Psychopharmacology.* 2003; 166(4):333–342. [PubMed: 12599023]
71. Gaisler-Salomon I, Diamant L, Rubin C, Weiner I. Abnormally persistent latent inhibition induced by MK801 is reversed by risperidone and by positive modulators of NMDA receptor function: differential efficacy depending on the stage of the task at which they are administered. *Psychopharmacology.* 2008; 196(2):255–267. [PubMed: 17928997]
72. Lipina T, Labrie V, Weiner I, Roder J. Modulators of the glycine site on NMDA receptors, D-serine and ALX 5407, display similar beneficial effects to clozapine in mouse models of schizophrenia. *Psychopharmacology.* 2005; 179(1):54–67. [PubMed: 15759151]
73. Labrie V, Lipina T, Roder JC. Mice with reduced NMDA receptor glycine affinity model some of the negative and cognitive symptoms of schizophrenia. *Psychopharmacology.* 2008; 200(2):217–230. [PubMed: 18597079]
74. Swerdlow NR, Geyer MA, Braff DL. Neural circuit regulation of prepulse inhibition of startle in the rat: current knowledge and future challenges. *Psychopharmacology.* 2001; 156(2–3):194–215. [PubMed: 11549223]
75. Ralph RJ, Varty GB, Kelly MA, et al. The dopamine D₂, but not D₃ or D₄, receptor subtype is essential for the disruption of prepulse inhibition produced by amphetamine in mice. *J Neurosci.* 1999; 19(11):4627–4633. [PubMed: 10341260]
76. Geyer MA, Krebs-Thomson K, Braff DL, Swerdlow NR. Pharmacological studies of prepulse inhibition models of sensorimotor gating deficits in schizophrenia: a decade in review. *Psychopharmacology.* 2001; 156(2–3):117–154. [PubMed: 11549216]
77. Brody SA, Conquet F, Geyer MA. Effect of antipsychotic treatment on the prepulse inhibition deficit of mGluR5 knockout mice. *Psychopharmacology.* 2004; 172(2):187–195. [PubMed: 14615875]

78. Ouagazzal AM, Jenck F, Moreau JL. Drug-induced potentiation of prepulse inhibition of acoustic startle reflex in mice: a model for detecting antipsychotic activity? *Psychopharmacology*. 2001; 156(2–3):273–283. [PubMed: 11549229]
79. Hagan JJ, Jones DN. Predicting drug efficacy for cognitive deficits in schizophrenia. *Schizophr Bull*. 2005; 31(4):830–853. [PubMed: 16177277]
80. Keefe RS, Eesley CE, Poe MP. Defining a cognitive function decrement in schizophrenia. *Biol Psychiatr*. 2005; 57(6):688–691.
81. Keefe RS, Sweeney JA, Gu H, et al. Effects of olanzapine, quetiapine, and risperidone on neurocognitive function in early psychosis: a randomized, double-blind 52-week comparison. *Am J Psychiatr*. 2007; 164(7):1061–1071. [PubMed: 17606658]
82. Black MD, Stevens RJ, Rogacki N, et al. AVE1625, a cannabinoid CB1 receptor antagonist, as a co-treatment with antipsychotics for schizophrenia: improvement in cognitive function and reduction of antipsychotic-side effects in rodents. *Psychopharmacology*. 2011; 215(1):149–163. [PubMed: 21181124]
83. Moore TL, Killiany RJ, Herndon JG, Rosene DL, Moss MB. A non-human primate test of abstraction and set shifting: an automated adaptation of the Wisconsin Card Sorting Test. *J Neurosci Methods*. 2005; 146(2):165–173. [PubMed: 16054506]
84. Dias R, Robbins TW, Roberts AC. Primate analogue of the Wisconsin Card Sorting Test: effects of excitotoxic lesions of the prefrontal cortex in the marmoset. *Behav Neurosci*. 1996; 110(5):872–886. [PubMed: 8918991]
85. Birrell JM, Brown VJ. Medial frontal cortex mediates perceptual attentional set shifting in the rat. *J Neurosci*. 2000; 20(11):4320–4324. [PubMed: 10818167]
86. Dias R, Aggleton JP. Effects of selective excitotoxic prefrontal lesions on acquisition of nonmatching- and matching-to-place in the T-maze in the rat: differential involvement of the prelimbic–infralimbic and anterior cingulate cortices in providing behavioural flexibility. *Eur J Neurosci*. 2000; 12(12):4457–4466. [PubMed: 11122356]
87. Arguello PA, Gogos JA. Cognition in mouse models of schizophrenia susceptibility genes. *Schizophr Bull*. 2010; 36(2):289–300. [PubMed: 20026558]
88. Coyle JT, Tsai G. The NMDA receptor glycine modulatory site: a therapeutic target for improving cognition and reducing negative symptoms in schizophrenia. *Psychopharmacology*. 2004; 174(1):32–38. [PubMed: 15205876]
89. Martina M, Gorfinkel Y, Halman S, et al. Glycine transporter type 1 blockade changes NMDA receptor-mediated responses and LTP in hippocampal CA1 pyramidal cells by altering extracellular glycine levels. *J Physiol*. 2004; 557(Pt 2):489–500. [PubMed: 15064326]
90. Tsai G, Ralph-Williams RJ, Martina M, et al. Gene knockout of glycine transporter 1: characterization of the behavioral phenotype. *Proc Natl Acad Sci USA*. 2004; 101(22):8485–8490. [PubMed: 15159536]
91. Singer P, Boison D, Möhler H, Feldon J, Yee BK. Enhanced recognition memory following glycine transporter 1 deletion in forebrain neurons. *Behav Neurosci*. 2007; 121(5):815–825. [PubMed: 17907814]
92. Yee BK, Balic E, Singer P, et al. Disruption of glycine transporter 1 restricted to forebrain neurons is associated with a procognitive and antipsychotic phenotypic profile. *J Neurosci*. 2006; 26(12):3169–3181. [PubMed: 16554468]
93. Singer P, Boison D, Möhler H, Feldon J, Yee BK. Modulation of sensorimotor gating in prepulse inhibition by conditional brain glycine transporter 1 deletion in mice. *Eur Neuropsychopharmacol*. 2011; 21(5):401–413. [PubMed: 20647165]
94. Kinney GG, Sur C, Burno M, et al. The glycine transporter type 1 inhibitor N-[3-(4'-fluorophenyl)-3-(4'-phenylphenoxy) propyl]sarcosine potentiates NMDA receptor-mediated responses *in vivo* and produces an antipsychotic profile in rodent behavior. *J Neurosci*. 2003; 23(20):7586–7591. [PubMed: 12930797]
- 95•. Möhler H, Boison D, Singer P, Feldon J, Pauly-Evers M, Yee BK. Glycine transporter 1 as a potential therapeutic target for schizophrenia-related symptoms: evidence from genetically modified mouse models and pharmacological inhibition. *Biochem Pharmacol*. 2011; 81(9):1065–

1077. Summarizes human and mouse findings of glycine transporter (GlyT1) inhibition relevant to schizophrenia resilience. [PubMed: 21333635]
96. Bergeron R, Meyer TM, Coyle JT, Greene RW. Modulation of *N*-methyl-D-aspartate receptor function by glycine transport. *Proc Natl Acad Sci USA*. 1998; 95(26):15730–15734. [PubMed: 9861038]
 97. Atkinson BN, Bell SC, De Vivo M, et al. ALX 5407: a potent, selective inhibitor of the hGlyT1 glycine transporter. *Mol Pharmacol*. 2001; 60(6):1414–1420. [PubMed: 11723250]
 98. Brown A, Carlyle I, Clark J, et al. Discovery and SAR of org 24598 – a selective glycine uptake inhibitor. *Bioorg Med Chem Lett*. 2001; 11(15):2007–2009. [PubMed: 11454468]
 99. Harsing LG Jr, Gacsalyi I, Szabo G, et al. The glycine transporter-1 inhibitors NFPS and Org 24461: a pharmacological study. *Pharmacol Biochem Behav*. 2003; 74(4):811–825. [PubMed: 12667895]
 100. Depoortère R, Dargazanli G, Estenne-Bouhtou G, et al. Neurochemical, electrophysiological and pharmacological profiles of the selective inhibitor of the glycine transporter-1 SSR504734, a potential new type of antipsychotic. *Neuropsychopharmacology*. 2005; 30(11):1963–1985. [PubMed: 15956994]
 101. Pinard E, Alanine A, Alberati D, et al. Selective GlyT1 inhibitors: discovery of [4-(3-fluoro-5-trifluoromethylpyridin-2-yl) piperazin-1-yl][5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methylethoxy)phenyl] methanone (RG1678), a promising novel medicine to treat schizophrenia. *J Med Chem*. 2010; 53(12):4603–4614. [PubMed: 20491477]
 102. Sasaki M, Konno R, Nishio M, Niwa A, Yasumura Y, Enami J. A single-base-pair substitution abolishes D-amino-acid oxidase activity in the mouse. *Biochim Biophys Acta*. 1992; 1139(4):315–318. [PubMed: 1355365]
 103. Hashimoto A, Konno R, Yano H, et al. Mice lacking D-amino acid oxidase activity exhibit marked reduction of methamphetamine-induced stereotypy. *Eur J Pharmacol*. 2008; 586(1–3):221–225. [PubMed: 18448092]
 104. Labrie V, Wong AH, Roder JC. Contributions of the D-serine pathway to schizophrenia. *Neuropharmacology*. 2012; 62(3):1484–1503. [PubMed: 21295046]
 105. Panizzutti R, Rausch M, Zurbügg S, Baumann D, Beckmann N, Rudin M. The pharmacological stimulation of NMDA receptors via co-agonist site: an fMRI study in the rat brain. *Neurosci Lett*. 2005; 380(1–2):111–115. [PubMed: 15854761]
 106. Konno R, Yasumura Y. Mouse mutant deficient in D-amino acid oxidase activity. *Genetics*. 1983; 103(2):277–285. [PubMed: 6131852]
 107. Wake K, Yamazaki H, Hanzawa S, et al. Exaggerated responses to chronic nociceptive stimuli and enhancement of *N*-methyl-D-aspartate receptor-mediated synaptic transmission in mutant mice lacking D-amino-acid oxidase. *Neurosci Lett*. 2001; 297(1):25–28. [PubMed: 11114476]
 108. Labrie V, Wang W, Barger SW, Baker GB, Roder JC. Genetic loss of D-amino acid oxidase activity reverses schizophrenia-like phenotypes in mice. *Genes Brain Behav*. 2010; 9(1):11–25. [PubMed: 19751394]
 109. Hashimoto A, Yoshikawa M, Niwa A, Konno R. Mice lacking D-amino acid oxidase activity display marked attenuation of stereotypy and ataxia induced by MK-801. *Brain Res*. 2005; 1033(2):210–215. Reviews animal data on D-amino acid oxidase mouse mutants and their relevance to schizophrenia resilience. [PubMed: 15694926]
 110. Zhang M, Ballard ME, Basso AM, et al. Behavioral characterization of a mutant mouse strain lacking D-amino acid oxidase activity. *Behav Brain Res*. 2011; 217(1):81–87. [PubMed: 20933022]
 111. Almond SL, Fradley RL, Armstrong EJ, et al. Behavioral and biochemical characterization of a mutant mouse strain lacking D-amino acid oxidase activity and its implications for schizophrenia. *Mol Cell Neurosci*. 2006; 32(4):324–334. [PubMed: 16843004]
 112. Labrie V, Duffy S, Wang W, Barger SW, Baker GB, Roder JC. Genetic inactivation of D-amino acid oxidase enhances extinction and reversal learning in mice. *Learn Mem*. 2009; 16(1):28–37. [PubMed: 19117914]

113. Maekawa M, Watanabe M, Yamaguchi S, Konno R, Hori Y. Spatial learning and long-term potentiation of mutant mice lacking D-amino-acid oxidase. *Neurosci Res.* 2005; 53(1):34–38. [PubMed: 15996778]
114. Tsai G, Yang P, Chung LC, Lange N, Coyle JT. D-serine added to antipsychotics for the treatment of schizophrenia. *Biol Psychiatr.* 1998; 44(11):1081–1089.
115. Heresco-Levy U, Javitt DC, Ebstein R, et al. D-serine efficacy as add-on pharmacotherapy to risperidone and olanzapine for treatment-refractory schizophrenia. *Biol Psychiatr.* 2005; 57(6): 577–585.
116. Gottlieb JD, Cather C, Shanahan M, Creedon T, Macklin EA, Goff DC. D-cycloserine facilitation of cognitive behavioral therapy for delusions in schizophrenia. *Schizophr Res.* 2011; 131(1–3): 69–74. [PubMed: 21723096]
117. Buchanan RW, Javitt DC, Marder SR, et al. The Cognitive and Negative Symptoms in Schizophrenia Trial (CONSIST): the efficacy of glutamatergic agents for negative symptoms and cognitive impairments. *Am J Psychiatr.* 2007; 164(10):1593–1602. [PubMed: 17898352]
118. Chung SP, Sogabe K, Park HK, et al. Potential cytotoxic effect of hydroxypyruvate produced from D-serine by astroglial D-amino acid oxidase. *J Biochem.* 2010; 148(6):743–753. [PubMed: 20876609]
119. Park HK, Shishido Y, Ichise-Shishido S, et al. Potential role for astroglial D-amino acid oxidase in extracellular D-serine metabolism and cytotoxicity. *J Biochem.* 2006; 139(2):295–304. [PubMed: 16452318]
120. Brandish PE, Chiu CS, Schneeweis J, et al. A cell-based ultra-high-throughput screening assay for identifying inhibitors of D-amino acid oxidase. *J Biomol Screen.* 2006; 11(5):481–487. [PubMed: 16760370]
121. Verrall L, Burnet PW, Betts JF, Harrison PJ. The neurobiology of D-amino acid oxidase and its involvement in schizophrenia. *Mol Psychiatr.* 2010; 15(2):122–137.
122. Yagi K, Nagatsu T, Ozawa T. Inhibitory action of chlorpromazine on the oxidation of D-amino-acid in the diencephalon part of the brain. *Nature.* 1956; 177(4515):891–892. [PubMed: 13321990]
123. Iwana S, Kawazoe T, Park HK, et al. Chlorpromazine oligomer is a potentially active substance that inhibits human D-amino acid oxidase, product of a susceptibility gene for schizophrenia. *J Enzyme Inhib Med Chem.* 2008; 23(6):901–911. [PubMed: 18615285]
124. Moghaddam B, Adams B, Verma A, Daly D. Activation of glutamatergic neurotransmission by ketamine: a novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. *J Neurosci.* 1997; 17(8):2921–2927. [PubMed: 9092613]
125. Razoux F, Garcia R, Léna I. Ketamine, at a dose that disrupts motor behavior and latent inhibition, enhances prefrontal cortex synaptic efficacy and glutamate release in the nucleus accumbens. *Neuropsychopharmacology.* 2007; 32(3):719–727. [PubMed: 16525415]
126. Takahata R, Moghaddam B. Activation of glutamate neurotransmission in the prefrontal cortex sustains the motoric and dopaminergic effects of phencyclidine. *Neuropsychopharmacology.* 2003; 28(6):1117–1124. [PubMed: 12700703]
127. Moghaddam B. Bringing order to the glutamate chaos in schizophrenia. *Neuron.* 2003; 40(5): 881–884. [PubMed: 14659087]
128. Karlsson RM, Tanaka K, Heilig M, Holmes A. Loss of glial glutamate and aspartate transporter (excitatory amino acid transporter 1) causes locomotor hyperactivity and exaggerated responses to psychotomimetics: rescue by haloperidol and metabotropic glutamate 2/3 agonist. *Biol Psychiatr.* 2008; 64(9):810–814.
129. Yizhar O, Fenno LE, Prigge M, et al. Neocortical excitation/inhibition balance in information processing and social dysfunction. *Nature.* 2011; 477(7363):171–178. [PubMed: 21796121]
130. Théberge J, Bartha R, Drost DJ, et al. Glutamate and glutamine measured with 4.0 T proton MRS in never-treated patients with schizophrenia and healthy volunteers. *Am J Psychiatr.* 2002; 159(11):1944–1946. [PubMed: 12411236]

131. Tibbo P, Hanstock C, Valiakalayil A, Allen P. 3-T proton MRS investigation of glutamate and glutamine in adolescents at high genetic risk for schizophrenia. *Am J Psychiatr.* 2004; 161(6): 1116–1118. [PubMed: 15169703]
132. Zoccali R, Muscatello MR, Bruno A, et al. The effect of lamotrigine augmentation of clozapine in a sample of treatment-resistant schizophrenic patients: a double-blind, placebo-controlled study. *Schizophr Res.* 2007; 93(1–3):109–116. [PubMed: 17383857]
133. Gaisler-Salomon I, Miller GM, Chuhma N, et al. Glutaminase-deficient mice display hippocampal hypoactivity, insensitivity to pro-psychotic drugs and potentiated latent inhibition: relevance to schizophrenia. *Neuropsychopharmacology.* 2009; 34(10):2305–2322. Describes GLS1-deficient mice as a model of schizophrenia resilience. [PubMed: 19516252]
134. Masson J, Darmon M, Conjard A, et al. Mice lacking brain/kidney phosphate-activated glutaminase have impaired glutamatergic synaptic transmission, altered breathing, disorganized goal-directed behavior and die shortly after birth. *J Neurosci.* 2006; 26(17):4660–4671. [PubMed: 16641247]
135. Cavazzuti M, Porro CA, Biral GP, Benassi C, Barbieri GC. Ketamine effects on local cerebral blood flow and metabolism in the rat. *J Cereb Blood Flow Metab.* 1987; 7(6):806–811. [PubMed: 3121648]
136. Gaisler-Salomon I, Wang Y, Chuhma N, et al. Synaptic underpinnings of altered hippocampal function in glutaminase-deficient mice during maturation. *Hippocampus.* 2012; 22(5):1027–1039. [PubMed: 22431402]
137. Schobel SA, Lewandowski NM, Corcoran CM, et al. Differential targeting of the CA1 subfield of the hippocampal formation by schizophrenia and related psychotic disorders. *Arch Gen Psychiatr.* 2009; 66(9):938–946. [PubMed: 19736350]
138. Flores C, Manitt C, Rodaros D, et al. Netrin receptor deficient mice exhibit functional reorganization of dopaminergic systems and do not sensitize to amphetamine. *Mol Psychiatr.* 2005; 10(6):606–612.
139. Manitt C, Mimee A, Eng C, et al. The netrin receptor DCC is required in the pubertal organization of mesocortical dopamine circuitry. *J Neurosci.* 2011; 31(23):8381–8394. [PubMed: 21653843]
140. Yetnikoff L, Eng C, Benning S, Flores C. Netrin-1 receptor in the ventral tegmental area is required for sensitization to amphetamine. *Eur J Neurosci.* 2010; 31(7):1292–1302. [PubMed: 20345916]
141. Srour M, Rivière JB, Pham JM, et al. Mutations in *DCC* cause congenital mirror movements. *Science.* 2010; 328(5978):592. [PubMed: 20431009]
142. Bibb JA. Decoding dopamine signaling. *Cell.* 2005; 122(2):153–155. [PubMed: 16051141]
143. Beaulieu JM, Sotnikova TD, Yao WD, et al. Lithium antagonizes dopamine-dependent behaviors mediated by an AKT/glycogen synthase kinase 3 signaling cascade. *Proc Natl Acad Sci USA.* 2004; 101(14):5099–5104. [PubMed: 15044694]
144. Beaulieu JM, Sotnikova TD, Marion S, Lefkowitz RJ, Gainetdinov RR, Caron MG. An Akt/beta-arrestin 2/PP2A signaling complex mediates dopaminergic neurotransmission and behavior. *Cell.* 2005; 122(2):261–273. [PubMed: 16051150]
145. Svenningsson P, Tzavara ET, Carruthers R, et al. Diverse psychotomimetics act through a common signaling pathway. *Science.* 2003; 302(5649):1412–1415. [PubMed: 14631045]
146. Allen JA, Yost JM, Setola V, et al. Discovery of β -arrestin-biased dopamine D2 ligands for probing signal transduction pathways essential for antipsychotic efficacy. *Proc Natl Acad Sci USA.* 2011; 108(45):18488–18493. [PubMed: 22025698]
147. Mallon AM, Blake A, Hancock JM. EuroPhenome and EMPReSS: online mouse phenotyping resource. *Nucleic Acids Res.* 2008; 36(Database issue):D715–D718. [PubMed: 17905814]
148. Dempster EL, Pidsley R, Schalkwyk LC, et al. Disease-associated epigenetic changes in monozygotic twins discordant for schizophrenia and bipolar disorder. *Hum Mol Genet.* 2011; 20(24):4786–4796. [PubMed: 21908516]
149. Ramboz S, Oosting R, Amara DA, et al. Serotonin receptor 1A knockout: an animal model of anxiety-related disorder. *Proc Natl Acad Sci USA.* 1998; 95(24):14476–14481. [PubMed: 9826725]

150. Ansorge MS, Zhou M, Lira A, Hen R, Gingrich JA. Early-life blockade of the 5-HT transporter alters emotional behavior in adult mice. *Science*. 2004; 306(5697):879–881. [PubMed: 15514160]
151. Giros B, Jaber M, Jones SR, Wightman RM, Caron MG. Hyperlocomotion and indifference to cocaine and amphetamine in mice lacking the dopamine transporter. *Nature*. 1996; 379(6566): 606–612. [PubMed: 8628395]
152. Gellman, C.; Mingote, S.; Wang, Y.; Gaisler-Salomon, I.; Rayport, S. Genetic pharmacotherapy. In: Kapetanovic, I., editor. *Drug Discovery and Development – Present and Future*. InTech; Rijeka, Croatia: 2011. p. 125-150.
153. Abbott A. Novartis to shut brain research facility. *Nature*. 2011; 480(7376):161–162. [PubMed: 22158218]
154. Chiamulera C, Epping-Jordan MP, Zocchi A, et al. Reinforcing and locomotor stimulant effects of cocaine are absent in mGluR5 null mutant mice. *Nat Neurosci*. 2001; 4(9):873–874. [PubMed: 11528416]
155. Heurteaux C, Lucas G, Guy N, et al. Deletion of the background potassium channel TREK-1 results in a depression-resistant phenotype. *Nat Neurosci*. 2006; 9(9):1134–1141. [PubMed: 16906152]
156. Zhang Y, Kurup P, Xu J, et al. Genetic reduction of striatal-enriched tyrosine phosphatase (STEP) reverses cognitive and cellular deficits in an Alzheimer's disease mouse model. *Proc Natl Acad Sci USA*. 2010; 107(44):19014–19019. [PubMed: 20956308]
157. Oliveira TG, Chan RB, Tian H, et al. Phospholipase d2 ablation ameliorates Alzheimer's disease-linked synaptic dysfunction and cognitive deficits. *J Neurosci*. 2010; 30(49):16419–16428. [PubMed: 21147981]
158. Tang YP, Shimizu E, Dube GR, et al. Genetic enhancement of learning and memory in mice. *Nature*. 1999; 401(6748):63–69. [PubMed: 10485705]
159. Cao X, Cui Z, Feng R, et al. Maintenance of superior learning and memory function in NR2B transgenic mice during ageing. *Eur J Neurosci*. 2007; 25(6):1815–1822. [PubMed: 17432968]
160. Gaisler-Salomon I, Wang Y, McKinney S, et al. Adult-onset glutamate receptor expression deficits in the hippocampus of glutaminase-deficient mice. *Biol Psychiatr*. 2010; 67:S71.

Key issues

- The etiology of schizophrenia remains elusive, which has made finding mechanistically based therapies challenging.
- Mouse models of neuropsychiatric disorders offer a way to validate genetic insights.
- Insight from pathogenesis is inherently limited in guiding the discovery of treatments to counter pathophysiology.
- Mouse models of resilience offer a way to validate pharmacotherapeutic approaches.
- Resilience mouse models may offer less insight into pathogenesis, but at the same time validate more directly applicable pharmacotherapeutic approaches.
- New treatment targets may offer novel insights into disease mechanisms, and *vice versa*.

Figure 1. The forces of vulnerability and resilience can push an individual towards disease or health

Vulnerability and resilience involve genetic, environmental and social forces.

Figure 2. Synaptic impact on glutamatergic transmission in the three schizophrenia resilience mouse models targeting N-methyl-D-aspartate receptor hypofunction

The models are shown in the columns, with the synaptic dynamics for the wt illustrated in the top row and the impact of the heterozygous reduction in the bottom row. In GlyT1 hets, synaptic glycine is increased, which acts at the glycine modulatory site of the NMDA receptor. Similarly, in DAO hets, D-serine is increased, which also acts at the glycine modulatory site. Both presumably counter NMDA receptor hypofunction to exert a resilience effect. In GLS1 hets, an activity-dependent reduction in synaptic glutamate release limits excessive stimulation of AMPA receptors, putatively conferring resilience. α-KA: α-keto acid; AMPA-R: AMPA receptor; D-SerT: D-serine transporter; DAO: D-amino acid oxidase; D-Ser: D-serine; Gln: Glutamine; Gls1: Glutaminase; Glu: Glutamate; GluT: Glutamate transporter; Gly: Glycine; GlyT1: Glycine transporter; GS: Glutamine synthase; L-Ser: L-serine; NMDA-R: N-methyl-D-aspartate receptor; SR: Serine racemase; wt: Wild type.

Table 1

Genetic mouse models of resilience to neuropsychiatric disorders other than schizophrenia.

Disorder	Genotype	Physiological phenotype	Behavioral phenotype	Ref.
Addiction	DAT KO	Lack of the molecular substrate for psychostimulant action (DAT)	Indifference to cocaine and amphetamine	[151]
	mGluR5 KO	Elimination of mGluR5 signaling No difference in DA receptor or <i>DAT</i> expression No difference in basal extracellular DA levels or cocaine-induced DA increase in the NAc	Absence of cocaine reinforcement Lacks cocaine locomotor stimulation	[154]
Depression	Kcnk-2 KO	Lack of a neurotransmitter-regulated background-potassium channel Attenuation of stress-induced increases in corticosterone Enhanced antidepressant-induced hippocampal neurogenesis Enhanced serotonin (5HT) neurotransmission, as if they were treated with antidepressants	Reduction in depression-associated behaviors in forced swim test, tail suspension test, conditioned suppression of motility, learned helplessness and novelty-suppressed feeding Antidepressants had no further behavioral effect	[155]
Alzheimer's disease	Step ₆₁ KO	Normalization of NMDA receptor function in 3xTg-AD Alzheimer's disease mouse model	Rescue of cognitive impairment in 3xTg-AD mice	[156]
	PLD2 KO	Blockade of the synaptotoxic effects of A β	Rescues memory deficits in SwAPP Alzheimer's disease mouse model	[157]
Age-related cognitive decline	Doogie (CaMKII-NR2B transgenic)	Enhanced NMDA receptor signaling Increased hippocampal long-term potentiation	Improved performance in novel object recognition, contextual and cued fear conditioning, spatial reference memory and spatial working memory T-maze task	[158,159]

DA: Dopamine; DAT: Dopamine transporter; KO: Knockout; NAc: Nucleus accumbens; NMDA: *N*-methyl-D-aspartate; SwAPP: Swedish mutant of the amyloid precursor protein.

Table 2

Resilience criteria and genetic mouse models of schizophrenia.

Criterion	Genotype		
	<i>GlyT1 deletion</i>	<i>DAOIGISIR</i>	<i>GLS1 het</i>
I: Attenuation of abnormalities induced by psychotropic drugs or manipulations	+ Resistant to PCP-induced elevation of locomotor activity [95]	Resistant to effects of genetic reduction in NMDA receptor on LI, social behavior and memory [108]	Resistant to amphetamine-induced locomotor activation
	Resistant to amphetamine disruption of PPI [90]	Resistant to methamphetamine [103] and MK801-induced locomotor activation [109]	Resistant to ketamine activation of frontal cortex [133]
	– Enhanced PPI disruption after MK801 [90]		
II: Antipsychotic drug-like profile at baseline	+ Forebrain-specific knockout of GlyT1 potentiates LI [92]	Enhanced PPI [110]	Potentiated LI, not reversed by clozapine [133]
	– No change in LI in GlyT1 ^{Telenceph} mice [91]	No change in PPI [111] No potentiation of LI [108]	No change in PPI [133]
III: Pro-cognitive phenotype	+ Enhanced novel object recognition, associative learning and behavioral flexibility [95]	Superior performance in spatial memory tasks Enhanced LTP [110,112,113]	Enhanced trace fear conditioning [Hazan L, Gaissler-Salomoni, Unpublished Data]
	–		Decreased delay fear conditioning [133] Reduced LTP [160]

DAO: D-amino acid oxidase; GlyT1: Glycine transporter; LI: Latent inhibition; LTP: Long-term potentiation; NMDA: N-methyl-D-aspartate; PCP: Phencyclidine; PPI: Prepulse inhibition.