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Prepulse Inhibition and Genetic Mouse Models of Schizophrenia

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Abstract

Mutant mouse models related to schizophrenia have been based primarily on the pathophysiology of schizophrenia, the known effects of antipsychotic drugs, and candidate genes for schizophrenia. Sensorimotor gating deficits in schizophrenia patients, as indexed by measures of prepulse inhibition of startle (PPI), have been well characterized and suggested to meet the criteria as a useful endophenotype in human genetic studies. PPI refers to the ability of a non-startling "prepulse" to inhibit responding to the subsequent startling stimulus or "pulse." Because of the cross-species nature of PPI, it has been used primarily in pharmacological animal models to screen putative antipsychotic medications. As techniques in molecular genetics have progressed over the past 15 years, PPI has emerged as a phenotype used in assessing genetic mouse models of relevance to schizophrenia. In this review, we provide a selected overview of the use of PPI in mouse models of schizophrenia and discuss the contribution and usefulness of PPI as a phenotype in the context of genetic mouse models. To that end, we discuss mutant mice generated to address hypotheses regarding the pathophysiology of schizophrenia and candidate genes (i.e., hypothesis-driven). We also briefly discuss the usefulness of PPI in phenotype-driven approaches in which a PPI phenotype could lead to "bottom up" approaches of identifying novel genes of relevance to PPI (i.e., hypothesis-generating).

Keywords

Prepulse inhibition; startle; schizophrenia; mouse models

I. Introduction

Prepulse inhibition (PPI) of startle is a cross-species measure that refers to the ability of a non-startling "prestimulus" to inhibit the response to a startling stimulus ([96]; neurobiological reviews [64,190]). There have been numerous reports of PPI deficits in schizophrenia patients (for review see [19,197]), their unaffected first degree relatives [29], and patients with schizotypal personality disorder [28]. In addition to decreased PPI observed in schizophrenia patients, several other neuropsychiatric disorders are associated with decreased PPI, including Obsessive-Compulsive Disorder [189], Tourette's syndrome [192], Huntington's disease [195], manic bipolar patients [153], Panic Disorder [129], and adults with autism [154]. Thus, while there are several neuropsychiatric disorders that display decreased PPI compared to normal controls, PPI deficits in schizophrenia patients are the best characterized and the most widely replicated [19,114,128,130,197].

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While the meaning of deficient or reduced PPI for an organism has been debated, Swerdlow et al. (2008) have argued persuasively that it is a useful psychophysiological process for basic studies in humans and animals to probe neural circuitry and as a pharmacological screen. Additionally, PPI of startle has been suggested as a potentially useful endophenotype with which to understand the genetics of schizophrenia [18], meeting the criteria outlined for a viable endophenotype by Turetsky and colleagues [205]. Specifically, the endophenotype should be heritable, present in unaffected relatives, associated with a disorder with good test re-test reliability, able to be measured rapidly and easily, and have a discrete neurobiological basis that is related to the pathophysiology and genetics of a disease [205]. Hence, many in the field of schizophrenia genetics have focused primarily on neurophysiological measures such as PPI, P50 auditory evoked suppression, antisaccade eye movement, mismatch negativity, and P300 event related potential [205]. The assertion that PPI may be a useful endophenotype in genetic studies of schizophrenia, combined with the observation that PPI has a strong genetic component in mice [55], suggests that PPI may be a useful behavioral phenotype to consider in genetic mouse models related to schizophrenia. While there are certainly many other symptoms and deficits observed across the heterogeneous group of patients with schizophrenia, PPI appears to be a viable endophenotype for genetic studies and thus a reasonable approach to investigate in animal models of the genetics of schizophrenia. Mutant mouse models related to schizophrenia have been based primarily on the pathophysiology of schizophrenia, the known effects of antipsychotic drugs, and candidate genes for schizophrenia. In this review, we provide a selected overview of PPI in mouse models of schizophrenia and discuss the contribution and usefulness of PPI as a phenotype in the context of genetic mouse models. In a 2002 review of genetic mouse models of PPI, Geyer et al. [66] summarize studies of strain differences in PPI, genetic mutants, and the pharmacology of PPI in mice. More recently, there have been two particularly relevant reviews on mouse models of susceptibility genes for schizophrenia [143] and mouse models of altered PPI [197]. Hence, in order to avoid redundancy with these previous reviews, in the current review we highlight a few of the approaches to genetic mouse models of schizophrenia and discuss some of the important caveats to these approaches. To that end, we discuss mutant mice generated to address hypotheses regarding the pathophysiology of schizophrenia and candidate genes (i.e., hypothesis driven). We also discuss the usefulness of PPI in phenotype-driven approaches in which a PPI phenotype could lead to “bottom up” approaches of identifying novel genes of relevance to PPI (i.e., hypothesis-generating).

How does prepulse inhibition relate to symptoms of schizophrenia?

Many reports in the literature argue that PPI in animals models the positive symptoms of schizophrenia. This conceptualization stems primarily from the observation that drug-induced deficits in PPI are produced by psychotomimetic drugs such as amphetamine and PCP, and that drug-induced PPI deficits are reversed by first generation antipsychotics, which are all dopamine D_2 receptor antagonists. In a recent review, Jones et al. [103] nicely outline the animal models that map onto the clinical symptoms of schizophrenia and accurately point out that there are no suitable animal analogs of hallucinations or delusions. Jones et al. [103] do suggest that two other “positive symptoms”, psychomotor agitation and grossly disorganized behavior, may be assessed in animals through measures of locomotor response to novelty and patterns of motor activity, respectively. The misconception that PPI is a measure of the positive symptoms of schizophrenia most likely stems from the fact that models of PPI deficits (e.g., pharmacological disruptions) have been relatively successful in predicting antipsychotic medications, which are fairly effective at treating the positive symptoms of schizophrenia and less effective, if at all, at treating the negative symptoms and cognitive deficits in schizophrenia. Historically, of course, most drug development efforts have focused on the identification of antipsychotic treatments for the positive symptoms of schizophrenia, given that only these criteria were used to evaluate potential treatments for use in patients with schizophrenia.

Attempts to correlate PPI deficits with positive and negative symptoms have yielded mixed results [200]. Some studies have reported negative correlations between PPI and thought disorder [139,151,152] or distractibility [109] in schizophrenia. In a recent study comparing cognitive function with PPI in over 300 subjects, there were no correlations between PPI and cognition as measured by traditional "pen and paper" tests (i.e., Wisconsin Card Sorting Task [WCST], California Verbal Learning Task, etc.), however, there was a positive relationship between PPI and Global Assessment of Function (GAF) and Independent Living scales [193]. Nevertheless, studies assessing behavioral measures reflecting cognitive constructs have demonstrated relationships to PPI performance. For example, converging evidence indicates that PPI is correlated with strategy formation and execution time in the Cambridge Neuropsychological Test Automated Battery (CANTAB) in healthy controls [12,43,68], a finding which should be further examined in patients with schizophrenia. Further work is needed to specify the aspect of cognitive function that might be best related to gating processes such as PPI [215]. For example, the CNTRICS (Cognitive Neuroscience measures of Treatment Response of Impaired Cognition in Schizophrenia) program funded by the National Institute of Mental Health considered PPI to provide a measure of the cognitive construct of "gain control" as a specific aspect of the perceptual abnormalities seen in patients with schizophrenia [83]. The series of CNTRICS workshops concluded that PPI may have utility as a biomarker for use in proof of concept studies of potential treatments for the cognitive deficits in schizophrenia that are not ameliorated by existing antipsychotic drugs.

Utility of prepulse inhibition measures in genetic models of schizophrenia

For the purpose of evaluating a genetic mouse model of schizophrenia, the more useful comparison to make is not between PPI and specific symptoms of schizophrenia but rather the relationship between a gene and the observable dependent measure, i.e., PPI. As mentioned above, PPI has been suggested to meet the criteria as an endophenotype for genetic studies of schizophrenia [205]. The approach of using endophenotypes in schizophrenia in genetic studies has greatly strengthened the ability to conduct cross-species translational studies by providing specific observables or endophenotypes for study in experimental animals (reviewed in [65], [80]). Useful endophenotypes in this context are measures that are observed in humans and can be measured in mice.

Hints to the role a gene may play in neural circuitry of PPI—Genetic manipulations have the potential to increase our understanding of the neural circuitry of neuropsychiatric disorders. A PPI deficit could indicate that the gene may be involved in the neural circuitry know to modulate PPI (e.g., cortical, limbic, striatal [190]); in other words it could function as a "surrogate measure for neural processes" as Swerdlow et al. [197] argue. For example, if a mouse is developed for a schizophrenia candidate gene with a relatively unknown function (or at least not an obvious relationship to schizophrenia pathology) and this mouse exhibits a PPI deficit, this may be an indication that limbic or striatal circuitry is altered. While a PPI deficit per se is not indicative of altered striatal or limbic circuitry, the presence of the deficit may suggest that these brain regions are affected by the genetic manipulation and provide a reasonable starting place for further hypothesis testing regarding the neurobiological implications of the genetic manipulation. Of course any evaluation of a PPI phenotype should be considered in the context of a thorough assessment of physical and sensory abnormalities (e.g., hearing loss), as pointed out in [66].

A pharmacological screen—Mutant mouse models offer the opportunity to screen putative antipsychotics that may involve a novel target. Most pharmacological studies of PPI are based primarily on the ability of a drug (e.g., dopamine D_2 antagonist) to reverse a drug-induced deficit in PPI (e.g., D_2 agonist; [64]. This approach can lead to what some have called "receptor tautology," meaning that a model based on the disruptive effects of a dopamine D_2

agonist may only be able to predict drugs that act as D_2 receptor antagonists. Using mutant mice to screen for putative antipsychotics may provide a means to develop novel drug targets. Several important examples of mutant mice being used to test putative antipsychotics are reviewed in subsequent sections.

A tool to study gene-environment interactions—Based on the diathesis-stress model of schizophrenia, which postulates that a genetic susceptibility coupled with environmental factors may be required for the full manifestation of the disease [79], studies of gene-environment interactions may be particularly informative for schizophrenia. Three ways in which genetics and environmental manipulations have been utilized in genetic mouse models are: (1) using a mutant (e.g., knockout, KO) to delineate the mechanism of an environmental manipulation; (2) rescuing a phenotype in a mutant with an environmental manipulation; or (3) potentiating or unmasking a phenotype in a genetic mutant with an environmental manipulation (i.e., addressing the two-hit model of schizophrenia). There are a few examples in which PPI has been a useful endpoint with which to assess gene-environment interactions in mouse models of schizophrenia. For example, maternal immune activation (MIA) with PolyI:C during mid-gestation typically leads to deficits in PPI in adult offspring [140,178]. Interleukin (IL)-6 KO dams exposed to MIA during mid-gestation are insensitive to the effects of MIA (i.e., exposed offspring do not show deficits in PPI; [181]). Hence, PPI in a genetic mutant (IL-6 KO mice) was used to determine the mechanism for the effects of immune activation on brain development. An example of a PPI phenotype being "rescued" in a KO mouse comes from studies in Phospholipase C –β1 KO mice, in which PPI deficits and locomotor hyperactivity were attenuated in KO mice by environmental enrichment or clozapine [137]. While these are examples in which a genetic manipulation and an environmental manipulation interact, not all of these are true examples of gene-environment interactions in the sense of a "two-hit" hypothesis for schizophrenia. A good example of the "two-hit" approach are nuclear receptor null Nurr1 heterozygous mice, which display reduced mesocortical and mesolimbic dopamine [50] and reduced PPI following postnatal isolation rearing, an effect not observed with either isolation rearing or genotype alone [51]. This study provides a good example of the utility of PPI in gene-environment models relevant to schizophrenia, specifically those designed to test the "two-hit" hypothesis for the etiology of schizophrenia. It should be kept in mind, however, that many studies assessing gene-environment effects are evaluating additive effects of two manipulations and must be interpreted with caution.

Evaluating the role of a susceptibility gene in schizophrenia pathology—When evaluating the role of a susceptibility gene implicated in the pathophysiology of schizophrenia, it is important to consider what criteria should be placed on a genetic/etiological model. In the present context, it is relevant to consider whether or not deficient PPI is a necessary phenotype with which to evaluate the usefulness of a targeted gene deletion of potential relevance to schizophrenia. Failure to see a PPI deficit in a mouse model may indicate a "false negative" particularly if other key behaviors relevant to schizophrenia are observed. For example, if a genetic mouse model shows deficits in social interaction and disturbances in performance on cognitive tasks such as attentional set shifting, but no differences in PPI, this does not indicate that the genetic model is not of relevance to schizophrenia. In other words, lack of a PPI phenotype should not "kill" a putative genetic model of schizophrenia. The likelihood of being able to represent all aspects of a heterogeneous disease in another species with a genetic mutation (most often a single gene deletion) is very rare if not impossible. In a recent review, Jones et al. [103] quote George Box, an industrial statistician, who said that "all models are wrong, some are useful" [16] and suggest that support for a model should be based on the convergence of data from multiple sources (e.g., many animal models, human genetic studies, etc.). Thus, no one phenotype should be considered as being neither necessary nor sufficient

to support a model for schizophrenia. Along these same lines, Swerdlow et al. [197] point out that schizophrenia patients with functional impairments may have PPI in the normal range because of the overlapping PPI distributions between healthy volunteers and schizophrenia patients, and thus an animal model should not be rejected based on "normal" PPI.

Alpha-7 (α7) nicotinic acetylcholine receptor (nAchR) KO mice provide a good example of a schizophrenia susceptibility gene in which mutant KO mice display some phenotypes of relevance to schizophrenia in the absence of a PPI phenotype. Based on a genetic association between the α7 nicotinic receptor and schizophrenia, decreased expression of α7 nicotinic receptors in brain regions associated with schizophrenia, and the high prevalence of smoking in schizophrenia patients, α7 nAChR KO mice have gained importance in our understanding of the pathophysiology of schizophrenia [56,134]. In fact, genetic studies have implicated the α7 nAchR gene (CHRNA7) in auditory P50 gating [57,119,135]. In an attempt to understand the relationship between auditory P50 gating and PPI, several groups have examined the relationship between the two forms of "gating" through correlational analysis in humans and rats (summarized in [145]). While P50 gating deficits and PPI deficits are reported in schizophrenia patients, often in the same group of patients, data from these studies suggest that there is a divergence of PPI and P50 gating measures in schizophrenia patients and healthy controls [20,145]. PPI and N40 gating, the rodent analog of P50 gating, also appear to diverge from each other when measured contemporaneously in rats [191]. Hence, the divergence of gating measures within schizophrenia patients and the overlapping distributions of PPI between schizophrenia patients and controls, suggests that PPI in animal models should not be used as the sole indicator of a schizophrenia-relevant phenotype. For example, α7 nAChR KO mice do not exhibit deficits in PPI [150]. They do, however, show impaired performance in delayed non-matching to sample tasks [52] and deficits in attention as measured by the 5-choice serial reaction time task [214]. Thus, the lack of a PPI phenotype in α7 nAChR KO mice should be evaluated in the context of other behaviors relevant to schizophrenia in these mice, the strong association between α7 nAChR and auditory gating, and the divergence of gating measures in schizophrenia.

Along the same lines, there is the possibility that a PPI deficit in a mutant mouse model could represent a "false positive", in which a PPI phenotype may be suggestive of an association between that gene or pathway and schizophrenia and no such association is found. We would argue that the PPI phenotype should be interpreted as meaning that the given genetic manipulation may be involved in the regulation of PPI expression and caution that PPI phenotypes should not be automatically associated with schizophrenia. One example of a way to test for a "false positive" would be to examine whether or not the PPI deficit could be reversed with existing antipsychotic drugs.

II. Models of pathophysiology

Mutant mouse models of the pathophysiology of a disorder can be considered to reflect hypothesis-driven approaches. These models are based either on a known or a hypothesized neuropathology. The main approaches that will be reviewed here are based primarily on the pharmacology of psychotomimetic drugs, namely the glutamate and dopamine hypotheses of schizophrenia, and on evidence of GABA dysfunction in schizophrenia brains. Other approaches to modeling the pathophysiology of schizophrenia include mutants of specific proteins involved in neurodevelopment (e.g., Reelin, Synapsin II, STOP). While these approaches are extremely useful to our understanding of schizophrenia, they will not be reviewed here.

Glutamate

The glutamate hypothesis of schizophrenia is derived from evidence that acute administration of phencyclidine (PCP), a non-competitive N-methyl-D-aspartate (NMDA) antagonist, produces schizophrenia-like symptoms in healthy humans [98,101]. Extending such observations, several experimental studies have utilized another NMDA antagonist, ketamine, to induce a model psychosis in normal volunteers [1,113,146,207] and to exacerbate symptoms in patients with schizophrenia [132,133]. In rodents, extensive studies have examined the behavioral effects of NMDA antagonists and the ability of antipsychotic drugs to attenuate these effects. Of note, the PPI-disruptive effects of NMDA antagonists in rats appear to be largely insensitive to first generation antipsychotics but reduced by some second generation antipsychotics, mimicking the interactions observed in patients with schizophrenia (for review, see [63]). More recently, several different mutant mouse models have been created focusing on both NMDA and metabotropic glutamate receptors (mGluRs) as manipulations having specific relevance to the glutamate hypothesis of schizophrenia.

NMDA mutants—The NMDA receptor is composed of various conformations of multiple subunits (including NR1, NR2A-D, and NR3A-B). The most notable example of genetic mouse models of NMDA receptors is the NMDA receptor hypomorph mouse, in which the NR1 subunit of the NMDA receptor is markedly reduced. These mice exhibit substantial deficits in PPI compared to wildtype (WT) controls, which can be reduced by typical and atypical antipsychotic drugs [48,49,142]. Furthermore, these mice are more sensitive to the PPI-disruptive effects of amphetamine [142]. In another example, the NR3A subunit is transiently expressed during development and exists in low levels in adulthood. Although adult mice that overexpress the NR3A subunit exhibit normal PPI, male NR3A KO mice exhibit a transient increase in PPI during prepubertal development (i.e. 3–4 weeks postnatal), which may relate to developmental theories of glutamatergic involvement in schizophrenia [25]. Additionally, while NR2A KO mice do not display a PPI phenotype [17,183,199], NR2B KO mice show increased PPI [199].

Metabotropic glutamate receptor mutants—As a result of the model psychoses induced by antagonists of ionotropic NMDA glutamate receptors, interest has evolved in potential of pharmacological manipulations of glutamatergic synapses by targeting the metabotropic glutamate receptors. In one of the first such explorations, we identified a possible role of the type 5 metabotropic glutamate receptors (mGluR5) in PPI by using WT and mGluR5 KO mice backcrossed to two different background strains, 129SvPasIco and C57BL/6. In both strains, PPI was disrupted dramatically in the mGluR5 KO mice throughout a range of interstimulus intervals and sensory modalities [23]. Additional experiments in mGluR5 KO indicated that the PPI deficit in mGluR5 KO mice was independent of changes in baseline startle, mothering behavior, or breeding strategy and was not mimicked by acute administration of the mGluR5 antagonist MPEP [24]. Although the antipsychotic drugs raclopride and clozapine and the selective 5-HT2A antagonist M100907 failed to attenuate PPI deficits in mGluR5 KO mice [22], subsequent research has shown that subchronic treatment with clozapine attenuates the PPI deficits in mGluR5 KO mice [82]. Additionally, PPI deficits, as well as latent inhibition deficits, in mGluR5 KO mice are reversed with the ampakine CX546 [123], suggesting the efficacy of a novel therapeutic target for schizophrenia. Another mutant of the metabotropic glutamate receptor I family, mGluR1 KO mice, also display decreased PPI compared to WT littermates, which was reversed with the mood stabilizer lamotrigine but not the dopamine antagonist raclopride [21]. Thus, the PPI deficits in mGluR5 and mGluR1 KO mice appear to be insensitive to traditional antipsychotics, but more responsive to chronic clozapine. Thus, the metabotropic glutamate receptor I family may offer a novel target for antipsychotic drugs acting upon the glutamate system.

Homer mutants—Homer proteins are scaffolding proteins that are part of the postsynaptic density and are involved in synaptogenesis and receptor trafficking [53,209]. Homer proteins play important roles in glutamate synapses, in particular the clustering of mGluRs at dendritic synapses by linking mGluR proteins together [3,38]. In addition to alterations in memory, anxiety, and reward function, Homer1 KO mice display deficits in PPI that can be reversed by haloperidol [198] and "rescued" with adeno-associated virus delivery of the Homer 1c isoform to the prefrontal cortex [125]. Homer1 KO mice also show elevations in prefrontal cortical glutamate levels [198], which are also reversed by the Homer 1c isoform [125]. Subsequent studies on Homer1 KO mice tested at a later age than those in the Szumlinski et al. (2005) study, however, reported no differences in PPI [97].

Glycine mutants—The NMDA receptor complex is a ligand-gated ion channel, which contains several distinct modulatory sites [136]. PCP binds to a site located within the ion channel and acts as a non-competitive antagonist. Glycine binds to a site on the NMDA receptor complex and serves as a co-agonist at NMDA receptors [102]. Synaptic concentrations of glycine are regulated by glycine type 1 transporters (GLYT1), which are co-localized with NMDA receptors in forebrain and hippocampus (reviewed in [99]. The observation that glycine serves as a co-agonist and regulates NMDA receptor function has stimulated research on the therapeutic potential of targets for the glycine site on the NMDA receptor complex. In preclinical studies, glycine agonists and GLYT1 inhibitors have been shown to reverse both behavioral and neurochemical effects of PCP [99,100]. Specific to PPI, glycine transporter inhibitors reverse PPI deficits in adult rats sustaining neonatal ventral hippocampal lesions in [118] and dizocilpine-induced PPI deficits in mice [122]. Glycine site agonists have shown inconsistent effects on PPI, with glycine and D-serine but not D-cycloserine reversing dizocilpine-induced PPI deficits in mice in one study [106], and D-serine failing to block dizocilpine-induced PPI deficits in mice in another study [122]. Several clinical trials have investigated the efficacy of glycine agonists (e.g., glycine, D-serine, D-cycloserine) as adjuncts to antipsychotic treatment. D-serine has demonstrated efficacy in reducing positive, negative, and cognitive symptoms when added to ongoing antipsychotic treatment in schizophrenic patients [203]. D-cycloserine has been shown to improve negative symptoms when added to antipsychotic therapy in some clinical trials [72,73], but failed to show improvement in other trials [71,206].

Based on these pharmacological studies in animals and humans, several glycine receptor mutant mice have been created for behavioral and neurochemical studies. Mice with point mutations of the glycine site on the NMDA receptor, heterozygous Grin1(D481N/K483Q) mice, show decreased LTP, increased dopamine and serotonin function, deficient learning in the Morris water maze, and non-habituating hyperactivity [4]. Although their acoustic startle response is higher than WT controls, they display no difference in PPI. Interestingly, hyperactivity in the Grin1 mutants was not significantly attenuated with clozapine at doses that reduced activity in WT mice, suggesting that the mice were less sensitive to clozapine.

Glycine transporter 1 (GlyT1) KO mice display improved performance on hippocampal-dependent memory tasks and no difference in baseline PPI [202]. Interestingly, GlyT1 KO mice are less sensitive to PPI reductions induced by amphetamine but not dizocilpine, contrary to the reports of GlyT1 inhibitors blocking dizocilpine-induced reductions in PPI. D-amino acid oxidase (DAO) degrades D-serine and has been implicated as a candidate gene for schizophrenia by genetic association studies. Mice with a naturally occurring mutation (ddY/DAO-) lack DAO and have increased extracellular levels of D-serine [2]. These mice display slightly higher acoustic startle but no differences in PPI. In locomotor tests, however, ddY/DAO- mice were resistant to the locomotor-stimulating effects of PCP [2]. Thus, mutations or gene deletions that result in increased extracellular levels of glycine or D-serine have at least

partially corroborated the studies of the efficacy of glycine agonists in pharmacological and developmental disruptions of PPI.

Dopamine

The dopamine hypothesis of schizophrenia was formulated close to 50 years ago and is based on the observation that dopamine agonists such as amphetamine can produce psychotic symptoms and that all clinically effective antipsychotics are dopamine D_2 receptor antagonists [41,60,169,174].

DAT KO mice—Mice lacking the dopamine transporter (DAT) gene display markedly increased levels of dopamine [70], deficits in sensorimotor gating [5,160,164], and hyperactivity relative to WT mice [58,70,164,182]. PPI deficits in DAT KO mice can be reversed with either D_1 or D_2 dopamine antagonists [164], the 5-HT_{2A} antagonist M100,907 [5], the atypical antipsychotics clozapine and quetiapine [160], as well as antidepressant drugs such as serotonin- or norepinephrine-selective reuptake inhibitors and monoamine transporter inhibitors such as cocaine [210]. Thus, DAT KO mice may provide a useful animal model for predicting the efficacy of novel drugs in treating psychiatric illnesses characterized by a dysregulated DA system. On the other hand, since general monoamine transporter inhibition appears to attenuate PPI deficits in DAT KO mice, this model may produce false positives when using it as a screen for antipsychotic medications.

GABA

GABA dysfunction in schizophrenia—Recent research has identified subtle neuronal abnormalities of GABAergic systems in schizophrenia brains. There is a decrease in the number of non-pyramidal cells in prefrontal cortex, anterior cingulate, and hippocampus (reviewed in [8]). These cells are typically GABAergic cells, which could lead to a loss of inhibitory modulation in these brain regions (reviewed in [8]). Indeed, GABAergic interneurons are dysfunctional in a number of brain regions in schizophrenia [120,9]. Deficits in γ-aminobutyric acid (GABA)-containing neurons are consistently reported, particularly in the frontal cortex [6], [7] and hippocampus [216,10]. Benes et al. [10] reported significantly reduced density of interneurons in CA2 and CA3 of brains of schizophrenia patients, including drug-free patients, suggesting that deficits in interneurons may play a contributory role in the pathophysiology of schizophrenia. Consistent with this interpretation, neurochemical studies demonstrated a deficit of GABAergic uptake sites in the hippocampus [167], while other reports showed a widespread compensatory up-regulation of post-synaptic specific $GABA_A$ receptor binding activity throughout most sub-fields of the hippocampal formation [11] of schizophrenia patients. Therefore, there is substantial evidence for a functional impairment of GABAergic inhibitory interneurons in the hippocampus in schizophrenia [9,166]. These GABAergic deficits in schizophrenia could well be an initial deficit, perhaps of neurodevelopmental origin, that subsequently results in further progressive neuronal dysfunction and the development of schizophrenia in the second or third decade of life. These GABAergic deficits are unrelated to antipsychotic drug treatment, age, or duration of illness. We have shown a similar structural abnormality in rats that were reared in isolation and exhibit deficient PPI [88], providing further evidence that early environment plays an important role in normal neuronal development.

Several lines of evidence indicate that $GABA_A$ receptors (specifically, the alpha3 and alpha5 subunit-containing $GABA_A$ receptors) may be useful targets in the treatment of schizophrenia [141]. As noted above, markers for GABAergic interneurons are reduced in schizophrenia and in the hippocampus of isolation-reared rats. The alpha5 subunit of the $GABA_A$ receptor is specifically expressed in hippocampal and cortical neurons. Receptors containing the alpha5 subunit make up 15–20% of the $GABA_A$ receptors in the hippocampus, are extrasynaptic, and modulate temporal and spatial memory functions (reviewed in [141]). Several different alpha5

$GABA_A$ receptor inverse agonists have recently been shown to be cognitive enhancers in the delayed matching to position version of the water maze [34,44,186]. Mice with a partial deficit of alpha5 $GABA_A$ receptor in hippocampus (alpha5(H105R) point-mutation) showed improved performance in trace fear conditioning, a hippocampal-mediated task [42] and a resistance to extinction of conditioned fear [212]. These mice also show reductions in PPI and locomotor hyperactivity [89] and decreased latent inhibition [61]. Alpha3 containing $GABA_A$ receptor KO mice display deficits in PPI, which are normalized by haloperidol [213]. Additional GABAergic mutants include GABA transporter 1 and GAD65 KO mice. GAT1 KO mice exhibit decreased PPI in addition to reductions in open field activity [37]. Glutamic acid decarboxylase 65 (GAD65) KO mice lack the GABA synthesizing enzyme GAD65 and show decreased PPI [92].

This review of mutant mouse models of the pathophysiology of schizophrenia is not meant to be exhaustive. Many other mouse mutants of relevance to schizophrenia such as second messenger systems (e.g., CaMKIV, PLCB1) and neuropeptides (e.g., neurotensin, CRF) have been created and evaluated for alterations in PPI. The readers are referred to the recent review by Swerdlow et al. [197] for a description of these mutants.

III. Genetic mouse models as pharmacological tools

Historically, animal models of relevance to schizophrenia have been driven primarily by studies combining pharmacological inducing conditions (e.g., PCP) paired with relevant dependent measure(s) (e.g., PPI, locomotor hyperactivity; latent inhibition). Most of that literature is based on studies in rats and is reviewed extensively elsewhere [67]. These pharmacological models have been instrumental in establishing three of the most prominent theories of schizophrenia, the dopamine hypothesis [40,175], the serotonin (or serotonin-dopamine) hypothesis [15,81], and the glutamate hypothesis [81,113]. More recent attempts to develop models of relevance to schizophrenia involve genetic mouse models (reviewed in [66,143,197]). As noted below, in translating what we have learned about the pharmacology of rat PPI to that of genetic mouse models we must keep in mind several important differences between the pharmacology of mouse vs. rat PPI, since the models themselves have been built on rat pharmacology.

While none of the dopamine receptor KO mice (e.g., D_1, D_2, D_3, D_4, D_5) show PPI phenotypes per se, dopamine receptor mutant mice have proven useful to dissect the pharmacological profile of dopamine agonists in the disruption of PPI. The pharmacology of dopamine effects on PPI in mice is complex. For example, mice are less sensitive to the PPI-disruptive effect of dopamine D_2 receptor agonists than are rats [162,163]. Strain comparisons of dopamine agonists suggest that many strains, including one of the most commonly studied background strains C57BL/6 mice, are not sensitive to the PPI-disruptive effects of dopamine D_2 agonists [163]. Data from our laboratory suggest that the D_1 receptor plays a more important role in the modulation of PPI in mice compared to rats. For example, direct acting dopamine agonists such as apomorphine [162] and indirect dopamine agonists such as cocaine disrupt PPI primarily via D_1 receptors [45]; whereas D_2 receptors appear to modulate amphetamine-induced PPI deficits [165] and only partially mediate PPI disruptions induced by cocaine [45]. In contrast, both apomorphine- and amphetamine-induced PPI disruptions in rats are blocked by dopamine D_2 antagonists [64]. Thus, dopamine receptor KO mice have aided in our understanding of the pharmacological effects of dopamine agonists on PPI. Additionally, selective D_2 agonists such as quinpirole reduce PPI in rats (with differing sensitivities to the PPI disruptive effects depending on the strain and the prepulse to pulse interval [194,196, 208]), whereas selective D_1 agonists do not disrupt PPI in rats on their own (or do so only weakly) [64,163,194]. Thus, while dopamine agonist-induced disruptions of PPI in rats vary

depending on the interstimulus intervals and the strain, there does appear to be a species difference in the relative D1 vs D2 contribution to PPI disruption with dopamine agonists.

As with the dopamine system, some serotonergic drugs have been found to produce different and even opposite effects on PPI in rats and mice. Specifically, while 5-HT_{1A} agonists decrease PPI in rats [180], the same 5-HT_{1A} agonists (e.g., 8-OH-DPAT) increase PPI in mice [47]. Furthermore, indoleamine hallucinogens such as psilocin and 5-MeO-DMT increase PPI in mice [159] while decreasing PPI in rats [112]. Mutant mouse lines lacking specific serotonin receptor subtypes have been particularly useful in delineating the respective contributions of specific serotonin receptors to the effects of serotonin agonists on PPI (reviewed in [47,66]). Similarly, mutants of specific subunits of the $GABA_A$ receptor have been extremely useful in dissecting the effects of drugs acting at each of these subunits [171]. For example, studies using mice with a point mutation in the alpha1-containing subunit demonstrated that the sedative properties, but not the anxiolytic properties, of benzodiazepines were mediated by the alpha1 subunit [171]. A similar approach could be taken with known or putative antipsychotics. Overall, pharmacological disruptions of PPI and their reversal with antipsychotics have been better characterized in rats than in mice, although the literature on PPI pharmacology in mice is rapidly increasing [197]. In order to use mutant mouse models to examine the receptor mechanisms for alterations in PPI, more complete dose response studies are warranted in mice.

IV. Candidate gene approach: “Top-Down” Approach

Heritability estimates for schizophrenia range from 24–80% depending on whether the studies used diagnosis or endophenotypes in the estimations [32,84,188]. Linkage studies have identified several chromosomal regions and candidate genes thought to be involved in the pathogenesis of the disease (reviewed in [86,87,187]). As the field of schizophrenia genetics has developed, several gene targets have been identified consistently and have thus been modified in mouse models through gene deletion or the addition of a transgene. When evaluating candidate genes for mouse models, one should consider that many single nucleotide polymorphisms (SNPs) identified in genetic screens for schizophrenia involve mutations in introns of genes. Thus, it is very important to consider (1) whether or not functional mutations in the gene have been identified before embarking on mutant mouse models, and (2) the impact of species-specific alterations in gene function in the mutant mouse [126]. For the purposes of this review, our discussion is limited to a few of the candidate genes that have been associated with schizophrenia, namely neuregulin, COMT, and DISC-1.

Neuregulin

Neuregulin is a family of peptides related to an epidermal growth factor that is coded for by four different genes (NRG1-4). Genetic association studies have identified NRG1 as a susceptibility gene for schizophrenia [85,185]. NRG1 binds to the tyrosine kinase receptor ErbB4 [26]. The neuregulin family of peptides is expressed widely during development and plays an important role in neuronal migration, axon guidance, glial cell development, and synapse formation [138]. Neuregulins are also expressed in the adult brain, where they play a role in adult neurogenesis and can affect neuronal activity [138]. Neuregulin is conceptualized as a crucial player in a family of interacting genes that contribute to the development of neuronal systems involving NMDA, GABAergic, α7 nAChR, and other receptors in brain. NRG1 is a large peptide and thus several different mutant mouse models have been created for NRG1 as well as its receptor target ErbB4, with varying effects on brain development and behavior [62,77,143,168]. While the NRG1 gene deletion is lethal, behavioral and neuroanatomical studies have been conducted on NRG1 heterozygotes. For example, NRG1 and ErbB4 heterozygotes show reduced NMDA receptor expression and abnormal behavior [36,185]. Specifically, type III NRG1 heterozygotes (NRG1(tm1.1Lwr+/−)) show PPI deficits that are accompanied by enlarged lateral ventricles, prefrontal cortex hypofunction, and deficits in

delayed alternation memory tasks [36]. Thus the type III NRG1 heterozygotes represent a mouse model of a candidate gene for schizophrenia that shows several phenotypes of relevance to schizophrenia. Neuregulin interacts with the α7 nAChR, which has long been implicated in gating mechanisms [56]. The deficits in PPI in type III NRG1 heterozygous mice are reversed by subchronic administration of nicotine [36], mimicking the nicotine-induced improvement in PPI we have reported in healthy and schizophrenic humans [158].

Initial reports indicated that mice heterozygous for gene deletion of the Nrg1 transmembrane domain displayed PPI deficits [185]. These initial studies also reported that there were no differences in PPI between WT and KO ErbB4 mice [185]. Subsequent studies, however, reported some baseline behavioral differences in mice heterozygous for gene deletion of the NRG1 transmembrane domain, such as increased locomotor activity and investigatory behavior, and decreased anxiety-like behavior, but no baseline difference in PPI [14]. When challenged with tetrahydrocannabinol, however, NRG1 heterozygotes were slightly more sensitive to the PPI-enhancing effects of tetrahydrocannabinol [14]. Similar mice heterozygous for the NRG1 transmembrane domain show hyperactivity and some evidence of increased anxiety-like behavior [108] and decreased social novelty behavior [144]. Mice heterozygous for a mutation in the immunoglobulin (Ig) –like domain (Ig-nrg-1) show impaired latent inhibition and an increased sensitivity to the locomotor-decreasing effects of clozapine, but showed no differences in locomotor activity [168]. Based on previous unpublished reports of no PPI phenotype in similar mice with mutations of the NRG1 Ig domain, the authors did not test the mice in an acoustic startle/PPI paradigm [168]. Mice heterozygous for the NRG1 EGF-like domain are hyperactive in a novel environment and showed a potential increased sensitivity to the PPI-disruptive effects of dizocilpine, which was not supported by a statistically significant interaction between genotype and drug [46]. An interesting related mutant is the BACE1 (β-site APP-cleaving enzyme 1) KO mouse. Because of the role BACE1 plays in the "proteolytic processing" of NRG1, BACE-1 KO mice have been examined for neuroanatomical and behavioral differences relevant to schizophrenia. BACE-1 KO mice with impaired NRG1 show deficits in PPI, locomotor hyperactivity, increased sensitivity to dizocilpine, and reduced dendritic spine density in hippocampal pyramidal neurons [172].

Taken together, it appears that NRG1 heterozygotes have a varied phenotype depending on the targeted domain of the gene with the most consistent behavioral abnormality being locomotor hyperactivity. For more extensive reviews of the different NRG1 mutants that have been created and their resultant phenotypes see [46,143]. Overall, the PPI phenotype in NRG1 mutants has been inconsistent. Perhaps the most promising model that has shown abnormalities in multiple neuroanatomical and behavioral endpoints relevant to schizophrenia is the Type III NRG1 heterozygote mouse [36]. Based on the improvement in PPI with chronic nicotine in the mice, the Type III NRG1 heterozygotes may prove to be an interesting model against which to test novel therapeutic targets.

Catechol-O-Methyltransferase (COMT)

Chromosome 22q11 has been implicated in the genetics of schizophrenia based on the evidence that humans with 22q11.2 deletion have an increased risk for schizophrenia and that three of the genes implicated in schizophrenia, COMT, PRODH, and Gnb1L, lie within this chromosomal region [78,87,107]. In fact, microdeletions of 22q11.2 are among the most commonly known genetic risk factors for schizophrenia [124]. Some mouse models have been generated as potential models of the 22q11 gene deletion. For example, the Df1/+ mice display deficits in PPI and learning and memory [105]. While the approach of modeling the entire chromosomal deletion may be informative, another approach has been to target the specific susceptibility genes in that chromosomal region.

The COMT gene is one of the more robust genetic “hits” for schizophrenia [204]. COMT is involved in the catabolism of dopamine and norepinephrine at the synapse and heavily localized in the frontal cortex, where levels of DAT are low [176], and thus is the primary mode of dopamine metabolism in the frontal cortex. A SNP causing a missense mutation of codon 158 Valine (val) to Methionine (met) in the coding region was found in the human COMT gene [117,204]. The Val158Met polymorphism is a functional polymorphism, decreasing COMT enzymatic activity by 40% in the prefrontal cortex [35], increasing levels of dopamine in the prefrontal cortex and affecting many cognitive processes that are deficient in schizophrenia (e.g., working memory, attention, information processing, [204]; but see [184]]. COMT may be a susceptibility gene for schizophrenia, as Val158Met conferred an increased risk for developing schizophrenia in those individuals that smoked cannabis [33]. Recent evidence suggests that the COMT Val allele is associated with reduced P300 and P50 ERPs [59,76, 127] and reduced PPI [161,170], presumably due to decreased dopamine function in the prefrontal cortex. The PPI decreases observed with the COMT Val allele are attenuated with the COMT inhibitor tolcapone [69]. Studies also support the involvement of prefrontal cortex dopamine transmission in PPI across humans [90,91,115] and rodents [190], with decreased dopamine in prefrontal cortex or the administration of dopamine antagonists being associated with reductions in PPI.

To date, two approaches have been taken to model the genetic alterations in COMT observed in schizophrenia – both gene deletion [74,147,211] and a transgenic approach in which mice overexpress a human COMT-Val polymorphism [147]. COMT deficiency in mice increases dopamine signaling primarily in the prefrontal cortex but not in the dorsal striatum [74,211]. COMT KO mice do not display alterations in PPI [74,147], although startle magnitude was increased in COMT KO mice compared to COMT WT and heterozygous mice [147]. Similarly, COMT transgenic mice with the human COMT-Val polymorphism overexpressed do not show differences in PPI, although there is a trend for the mice to have decreased PPI [147]. In contrast, COMT-Tg mice do show disrupted attentional set shifting, working memory, and recognition memory [147]; whereas, COMT KO mice perform better on working memory tasks compared to their WT controls [147]. Thus, alterations in prefrontal cortex dopamine in these mice are associated with performance on cognitive tasks but not PPI. One issue to address, however, is that the human COMT-Val transgene was overexpressed in the presence of the mouse COMT gene. In these mice, the residual mouse COMT contributes to dopamine degradation, as does MAO. Compared to humans, MAO rather than COMT appears to play a major role in the degradation of dopamine in rodents [54,111]. Thus, while the data in COMT mutant mice clearly suggest that alterations in COMT gene can affect cognitive function, no clear relationship has been shown between COMT gene and PPI in mice.

Proline dehydrogenase (PRODH)

Another gene in the 22q11.2 region implicated in schizophrenia is proline dehydrogenase (PRODH). PRODH knockdown mice with reduced enzymatic activity of proline dehydrogenase have been shown to have reduced PPI [75]. In subsequent studies, PRODH knockdown mice backcrossed to a 129SvEv background exhibited an increase in glutamate release and alterations in COMT enzyme activity. The PRODH knockdown mice also displayed an increased sensitivity to the behavioral (increased locomotor activity) and neurochemical (increased dopamine release) effects of amphetamine, suggesting that there were functional interactions between the PRODH and COMT genes [148]. In these studies, PRODH knockdown mice showed no differences in baseline PPI, but did show PPI deficits when administered tolcapone, a COMT inhibitor, an effect not observed in WT mice [148].

Disrupted in Schizophrenia 1 (DISC1)

First identified in a Scottish pedigree, the Disrupted in Schizophrenia 1 (DISC1) gene has shown association with schizophrenia and behavioral and neuroanatomical biomarkers for schizophrenia (for review see [131,157]). The DISC1 gene was discovered through a cytogenetic approach, which identified a translocation between chromosome 1 and chromosome 11, a balanced t(1;11) (q42.1;q14.3) translocation, which was associated with schizophrenia and mood disorders (for review see [157]). DISC1 gene, encoding multiple isoforms of DISC1 protein [157] for review), was found to be disrupted by the breakpoint on chromosome 1. DISC1 isoforms appear to be cell-type-specific, are expressed throughout the brain (particularly regions implicated in schizophrenia such as the hippocampus), and are developmentally regulated [156]. Human imaging and behavioral studies have shown DISC1 to be functionally linked to schizophrenia. DISC1 is associated with abnormal P300 ERP [13], neurocognitive function (e.g., learning and memory; [27,31,93], and schizophrenia neuropathology such as reduced prefrontal gray matter [31] and reduced hippocampal size [30]. DISC1 protein interacts with several proteins that are important during neurodevelopment such as Ndel1, implicated in neuronal migration, and FEZ1, implicated in neurite extension [131]. DISC1 also interacts with phosphodiesterase 4B (PDE4B) to affect neuronal signaling via effects on cAMP levels [131].

Based on the strong genetic link between DISC1 and schizophrenia, several genetic mouse models have been created either via inducible transgenics or mutants with a missense mutation produced with by induced mutagenesis. For example, mice with a missense mutation in exon 2 of the DISC1 gene (L100P, and to a lesser extent Q31L, mutants) show decreased PPI and latent inhibition. PPI and latent inhibition phenotypes were reversed with antipsychotic drug treatment and rolipram, a PDE4 inhibitor, specifically in the L100P mutants [39]. These mice with missense mutations in the DISC1 gene also show evidence of overall decreased brain volume (9–13% reduction; [39]). Other DISC1 mutants have been generated by overexpressing a DISC1 transgene with temporal and/or regional specificity. For example, mice expressing a dominant negative form of the DISC1 gene under the αCaMKII promoter, which drives gene expression the forebrain, mainly pyramidal neurons of the cortex and hippocampus and granule cells of the dentate gyrus, display several phenotypes of relevance to schizophrenia [94]. Specifically, these mice have enlarged lateral ventricles, decreased parvalbumin immunoreactivity in the prefrontal cortex, locomotor hyperactivity, modest reductions in PPI, and increased immobility in the forced swim test [94]. The decreased PPI in the dominant negative DISC1 transgenic mice only occurs at one out of four prepulse intensities (74 dB). The use of relatively high prepulse intensities (74–90 dB), the lack of a strong intensity-dependent effect on PPI in control mice, and the high level of PPI (85% at the lowest prepulse intensity in control mice) make the PPI decrease difficult to interpret in these DISC1 transgenic mice. Further evaluation of the PPI phenotype would be needed to conclusively argue that these mice have reductions in PPI. Considering that these mice are slow to find a hidden food pellet [94], thought should be given to potential deficits in sensory detection and future tests of PPI should determine whether or not the putative PPI deficit is due to a hearing loss. Using a similar approach, Pletnikov et al. [155] generated a mouse with inducible expression of mutant human DISC1 under the control of the αCaMKII promoter. Consistent with previous studies, the mutant mice showed mild enlargement of lateral ventricles and decreased neurite outgrowth. Interesting sex-specific effects on behavior were observed. Male mutants showed increased locomotor activity and decreased social interaction; whereas females displayed decreased spatial memory in the probe test of the water maze. The mutant human DISC1 mice, however, did not display any alterations in PPI [155]. Mice with an inducible dominant negative DISC1 C-terminal fragment transiently expressed early in postnatal development (postnatal day 7) showed reduced hippocampal dendritic complexity and behavioral differences including impaired spatial working memory in a delayed nonmatch to place test, reduced social

interaction, and decreased time to immobility in the forced swim test [121]. These behavioral and neuronal phenotypes were apparent only after early postnatal induction of the DISC1 transgene and not when the DISC1 transgene was expressed in adulthood [121]. To our knowledge, PPI was not tested in these mice.

An alternative approach to unraveling the role of DISC1 in brain development is to conduct comparisons of the DISC1 gene across strains of mice. 129S6/SvEv mice carry a 25 bp deletion in exon 6 of the mouse DISC1 gene. C57BL6/J mice do not carry this deletion. Koike and colleagues [110] transferred the DISC1 mutated 129S6/SvEv allele to the C57BL6/J background. The resultant C57BL/6J mice with the DISC1 mutated allele showed altered neuronal morphology in hippocampus and prefrontal cortex [116] and impaired working memory as measured by a delayed non-match to place test [110,116]. The mutant DISC1 mice, however, did not differ from WT mice in locomotor activity, PPI, water maze performance, novel object recognition performance, or fear conditioning [110,116]. Yet another approach to modeling the DISC1 mutation has been to generate transgenic mice expressing two copies of a truncated form of DISC1 encoding the first 8 exons using a bacterial artificial chromosome (BAC) [177]. These mice display many of the phenotypes previously reported (e.g., enlarged lateral ventricles, reduced cerebral cortex, decreased parvalbumin in the prefrontal cortex, disrupted latent inhibition, increased immobility in the forced swim test) in addition to novel phenotypes including thinning of cortical layers II/III, decreased neuronal proliferation in developing cortex, reduced parvalbumin cells in the hippocampus, and reduced vocalizations in response to stress [177]. To our knowledge, PPI has not yet been assessed in these mice. Taken together, there is some limited evidence for the effects of altered DISC1 expression on PPI in mice. While some neuroanatomical and behavioral phenotypes appear to be somewhat consistent across the various DISC1 mutants, PPI does not appear to be a robust phenotype associated with alterations in DISC1 in mutant mouse models.

Making the appropriate mutant mouse for the DISC1 translocation has proven difficult, with many different strategies for modeling the genetic mutation in neuropsychiatric illness as described above. All of these models have been based on the hypothesis that the functional mutation in the human psychiatric conditions results from a truncated form of DISC1. However, the genetic mutation in the Scottish schizophrenia is not just the truncation of the DISC1 gene. A novel gene, termed Boymaw or DISC1FP1 (DISC1 Fusion Partner 1), was also found to be disrupted on chromosome 11. Two fusion transcripts are generated between DISC1 and Boymaw genes in the translocation carriers in the Scottish schizophrenia family [217]. Thus, expressing the two fusion transcripts would be a better strategy for creating mutant DISC1 mice for the study of neuropsychiatric disorders.

V. Hypothesis generating: “Bottom-Up” approach

What can a PPI phenotype tell us about novel genes for schizophrenia? The field of molecular genetics continues to produce new mutant mouse models with unknown effects on the central nervous system. Many of these mutants have behavioral abnormalities that have been observed anecdotally. One such example of the way a novel gene of relevance to psychiatric conditions can be discovered through the creation of a mutant mouse is the SP4 gene. SP4, a member of the Sp1 family of transcription factors, is expressed restrictively in the developing nervous system and most abundantly in adult hippocampus in mice. Hypomorphic Sp4 mice showed vacuolization in the hippocampus, age-dependent decrease in neurotrophin-3 expression in the dentate granule cells, and robust deficits in both PPI and contextual memory [218]. The restoration of Sp4 expression, via a Cre-dependent rescue strategy, completely rescued all the observed molecular, histological, and behavioral abnormalities [218]. These studies revealed a novel Sp4 pathway that is important for hippocampal development and essential to many behaviors, including PPI, relevant to schizophrenia [218]. Zhou and colleagues have gone on

to examine the role of the human SP4 gene in schizophrenia and bipolar disorder. Several SNPs from the human SP4 gene are found to associate with both bipolar disorder and schizophrenia in both Caucasian and Chinese samples [219]. This represents an example in which a PPI phenotype, in combination with other behavioral abnormalities, suggested the association of this gene with neuropsychiatric disorders. Similar "bottom-up" approaches have been taken through the use of inbred mouse strain comparisons [149], recombinant congenic mouse strains [104,201], selective breeding of mice and rats for high and low levels of PPI [95,173], and strain differences in the response to the pharmacological disruptions of PPI in rats [179,196].

While these types of "bottom-up" approaches would not directly implicate a given gene with schizophrenia, particularly since PPI deficits are not unique to schizophrenia, they may be useful in identifying genes or gene products relevant to the regulation of PPI expression. The phenotype, however, would suggest that the gene might be relevant to neuropsychiatric disorders in which PPI deficits have been observed.

VI. Discussion

Mutant mouse models of schizophrenia provide a unique way to assess the function of a susceptibility gene, test hypotheses about the pathophysiology of the disease, address treatment mechanisms of antipsychotic drugs, and generate hypotheses about the function of relatively unknown genes. In this review, we provided a brief overview of PPI deficits in some of these approaches and present specific examples where appropriate. As mentioned above, it is not likely that all aspects of a heterogeneous disease will be recapitulated in another species with a genetic mutation. Convergence of behavioral and neuroanatomical or neurochemical data in a given mutant mouse has been observed in several mutant mouse models (e.g., Type III NRG1 heterozygotes) and support clinical data on the link between the candidate gene and schizophrenia. As we point out throughout the review, no one phenotype such as PPI should be considered as being either necessary or sufficient to substantiate a model as having relevance to schizophrenia.

Future animal studies addressing schizophrenia would benefit greatly from more neurobiologically based biomarkers for schizophrenia. Such an approach has been taken in the CNTRICS initiative, in an explicit attempt to incorporate more cognitive neuroscience based testing into treatment trials of putative cognitive therapies for schizophrenia. Along the same lines, genetic studies of schizophrenia have focused on psychophysiological endophenotypes such as PPI instead of the broader, more heterogeneous diagnosis of schizophrenia. In fact, many laboratories are now using PPI as an endophenotype in genetic studies of schizophrenia [18,84]. Some of these genetic studies have generated further support for a genetic contribution to PPI [84], and other studies have suggested that genetic variants in COMT directly affect PPI levels (as reviewed above) [161,170]. Thus, as human studies materialize with more neurobiologically defined behavioral measures, the ability to translate these measures or "endophenotypes" to animal models should improve dramatically.

In this review, we assert that PPI in mutant mouse models related to schizophrenia offers a behavioral endpoint that has shown predictive validity in rat pharmacological models, cross species homology with the same measure in humans, and alterations in response to genetic manipulations implicated in the pathogenesis of schizophrenia. While these mutant mouse models are not without shortcomings, they offer some of the best attempts at etiological models that are possible in rodents. Merging the genetic etiological models with a second hit approach may strengthen some of the mutant mouse models. Hence, consideration for other factors, such as the importance of environmental risk factors (e.g., prenatal infection) and the role of epigenetics (e.g., DNA methylation) in the etiology of schizophrenia, should also be incorporated with genetic models.

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References

1. Abel KM, Allin MP, Hemsley DR, Geyer MA. Low dose ketamine increases prepulse inhibition in healthy men. Neuropharmacology 2003;44:729–737. [PubMed: 12681371]
2. Almond SL, Fradley RL, Armstrong EJ, Heavens RB, Rutter AR, Newman RJ, Chiu CS, Konno R, Hutson PH, Brandon NJ. Behavioral and biochemical characterization of a mutant mouse strain lacking d-amino acid oxidase activity and its implications for schizophrenia. Molecular and Cellular Neuroscience 2006;32:324–334. [PubMed: 16843004]
3. Ango F, Pin JP, Tu JC, Xiao B, Worley PF, Bockaert J, Fagni L. Dendritic and axonal targeting of type 5 metabotropic glutamate receptor is regulated by homer1 proteins and neuronal excitation. J Neurosci 2000;20:8710–8716. [PubMed: 11102477]
4. Ballard TM, Pauly-Evers M, Higgins GA, Ouagazzal A-M, Mutel V, Borroni E, Kemp JA, Bluethmann H, Kew JNC. Severe impairment of nmda receptor function in mice carrying targeted point mutations in the glycine binding site results in drug-resistant nonhabituating hyperactivity. J Neurosci 2002;22:6713–6723. [PubMed: 12151550]
5. Barr AM, Lehmann-Masten V, Paulus M, Gainetdinov RR, Caron MG, Geyer MA. The selective serotonin-2a receptor antagonist m100907 reverses behavioral deficits in dopamine transporter knockout mice. Neuropsychopharmacology 2004;29:221–228. [PubMed: 14603268]
6. Beasley CL, Reynolds GP. Parvalbumin-immunoreactive neurons are reduced in the prefrontal cortex of schizophrenics. Schizophr Res 1997;24:349–355. [PubMed: 9134596]
7. Beasley CL, Zhang ZJ, Patten I, Reynolds GP. Selective deficits in prefrontal cortical gabaergic neurons in schizophrenia defined by the presence of calcium-binding proteins. Biol Psychiatry 2002;52:708–715. [PubMed: 12372661]
8. Benes FM. Emerging principles of altered neural circuitry in schizophrenia. Brain Res Brain Res Rev 2000;31:251–269. [PubMed: 10719152]
9. Benes FM, Berretta S. Gabaergic interneurons: Implications for understanding schizophrenia and bipolar disorder. Neuropsychopharmacology 2001;25:1–27. [PubMed: 11377916]
10. Benes FM, Kwok EW, Vincent SL, Todtenkopf MS. A reduction of nonpyramidal cells in sector ca2 of schizophrenics and manic depressives. Biol Psychiatry 1998;44:88–97. [PubMed: 9646890]
11. Benes FM, Vincent SL, Marie A, Khan Y. Up-regulation of gabaa receptor binding on neurons of the prefrontal cortex in schizophrenic subjects. Neuroscience 1996;75:1021–1031. [PubMed: 8938738]
12. Bitsios P, Giakoumaki SG, Theou K, Frangou S. Increased prepulse inhibition of the acoustic startle response is associated with better strategy formation and execution times in healthy males. Neuropsychologia 2006;44:2494–2499. [PubMed: 16698050]
13. Blackwood DH, Fordyce A, Walker MT, St Clair DM, Porteous DJ, Muir WJ. Schizophrenia and affective disorders--cosegregation with a translocation at chromosome 1q42 that directly disrupts brain-expressed genes: Clinical and p300 findings in a family. American journal of human genetics 2001;69:428–433. [PubMed: 11443544]
14. Boucher AA, Arnold JC, Duffy L, Schofield PR, Micheau J, Karl T. Heterozygous neuregulin 1 mice are more sensitive to the behavioural effects of delta9-tetrahydrocannabinol. Psychopharmacology (Berl) 2007;192:325–336. [PubMed: 17333138]
15. Bowers MB Jr, Freedman DX. “Psychedelic” Experiences in acute psychoses. Arch Gen Psychiatry 1966;15:240–248. [PubMed: 5911238]
16. Box, G.; Draper, N. Empirical model building and response surfaces. John Wiley; 1987. p. 74
17. Boyce-Rustay JM, Holmes A. Genetic inactivation of the nmda receptor nr2a subunit has anxiolytic- and antidepressant-like effects in mice. Neuropsychopharmacology 2006;31:2405–2414. [PubMed: 16482087]

18. Braff DL, Freedman R, Schork NJ, Gottesman II. Deconstructing schizophrenia: An overview of the use of endophenotypes in order to understand a complex disorder. Schizophr Bull 2007;33:21–32. [PubMed: 17088422]
19. Braff DL, Geyer MA, Swerdlow NR. Human studies of prepulse inhibition of startle: Normal subjects, patient groups, and pharmacological studies. Psychopharmacology (Berl) 2001;156:234–258. [PubMed: 11549226]
20. Braff DL, Light GA, Swerdlow NR. Prepulse inhibition and p50 suppression are both deficient but not correlated in schizophrenia patients. Biol Psychiatry 2007;61:1204–1207. [PubMed: 17161386]
21. Brody SA, Conquet F, Geyer MA. Disruption of prepulse inhibition in mice lacking mglur1. The European journal of neuroscience 2003;18:3361–3366. [PubMed: 14686909]
22. Brody SA, Conquet F, Geyer MA. Effect of antipsychotic treatment on the prepulse inhibition deficit of mglur5 knockout mice. Psychopharmacology (Berl) 2004;172:187–195. [PubMed: 14615875]
23. Brody SA, Dulawa SC, Conquet F, Geyer MA. Assessment of a prepulse inhibition deficit in a mutant mouse lacking mglu5 receptors. Mol Psychiatry 2004;9:35–41. [PubMed: 14699440]
24. Brody SA, Geyer MA. Interactions of the mglur5 gene with breeding and maternal factors on startle and prepulse inhibition in mice. Neurotox Res 2004;6:79–90. [PubMed: 15184109]
25. Brody SA, Nakanishi N, Tu S, Lipton SA, Geyer MA. A developmental influence of the n-methyl-d-aspartate receptor nr3a subunit on prepulse inhibition of startle. Biol Psychiatry 2005;57:1147–1152. [PubMed: 15866554]
26. Bublil EM, Yarden Y. The egf receptor family: Spearheading a merger of signaling and therapeutics. Current opinion in cell biology 2007;19:124–134. [PubMed: 17314037]
27. Burdick KE, Hodgkinson CA, Szeszko PR, Lencz T, Ekholm JM, Kane JM, Goldman D, Malhotra AK. Disc1 and neurocognitive function in schizophrenia. Neuroreport 2005;16:1399–1402. [PubMed: 16056147]
28. Cadenhead KS, Geyer MA, Braff DL. Impaired startle prepulse inhibition and habituation in patients with schizotypal personality disorder. Am J Psychiatry 1993;150:1862–1867. [PubMed: 8238643]
29. Cadenhead KS, Swerdlow NR, Shafer KM, Diaz M, Braff DL. Modulation of the startle response and startle laterality in relatives of schizophrenic patients and in subjects with schizotypal personality disorder: Evidence of inhibitory deficits. Am J Psychiatry 2000;157:1660–1668. [PubMed: 11007721]
30. Callicott JH, Straub RE, Pezawas L, Egan MF, Mattay VS, Hariri AR, Verchinski BA, Meyer-Lindenberg A, Balkissoon R, Kolachana B, Goldberg TE, Weinberger DR. Variation in disc1 affects hippocampal structure and function and increases risk for schizophrenia. Proc Natl Acad Sci U S A 2005;102:8627–8632. [PubMed: 15939883]
31. Cannon TD, Hennah W, van Erp TG, Thompson PM, Lonnqvist J, Huttunen M, Gasperoni T, Tuulio-Henriksson A, Pirkola T, Toga AW, Kaprio J, Mazziotta J, Peltonen L. Association of disc1/trax haplotypes with schizophrenia, reduced prefrontal gray matter, and impaired short-and long-term memory. Arch Gen Psychiatry 2005;62:1205–1213. [PubMed: 16275808]
32. Cardno AG, Gottesman II. Twin studies of schizophrenia: From bow-and-arrow concordances to star wars mx and functional genomics. American journal of medical genetics 2000;97:12–17. [PubMed: 10813800]
33. Caspi A, Moffitt TE, Cannon M, McClay J, Murray R, Harrington H, Taylor A, Arseneault L, Williams B, Braithwaite A, Poulton R, Craig IW. Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-o-methyltransferase gene: Longitudinal evidence of a gene x environment interaction. Biol Psychiatry 2005;57:1117–1127. [PubMed: 15866551]
34. Chambers MS, Atack JR, Carling RW, Collinson N, Cook SM, Dawson GR, Ferris P, Hobbs SC, O'Connor D, Marshall G, Rycroft W, MacLeod AM. An orally bioavailable, functionally selective inverse agonist at the benzodiazepine site of gabaa α5 receptors with cognition enhancing properties. J Med Chem 2004;47:5829–5832. [PubMed: 15537339]
35. Chen J, Lipska BK, Halim N, Ma QD, Matsumoto M, Melhem S, Kolachana BS, Hyde TM, Herman MM, Apud J, Egan MF, Kleinman JE, Weinberger DR. Functional analysis of genetic variation in catechol-o-methyltransferase (comt): Effects on mrna, protein, and enzyme activity in postmortem human brain. American journal of human genetics 2004;75:807–821. [PubMed: 15457404]

36. Chen Y-JJ, Johnson MA, Lieberman MD, Goodchild RE, Schobel S, Lewandowski N, Rosoklija G, Liu R-C, Gingrich JA, Small S, Moore H, Dwork AJ, Talmage DA, Role LW. Type iii neuregulin-1 is required for normal sensorimotor gating, memory-related behaviors, and corticostriatal circuit components. J Neurosci 2008;28:6872–6883. [PubMed: 18596162]
37. Chiu CS, Brickley S, Jensen K, Southwell A, McKinney S, Cull-Candy S, Mody I, Lester HA. Gaba transporter deficiency causes tremor, ataxia, nervousness, and increased gaba-induced tonic conductance in cerebellum. J Neurosci 2005;25:3234–3245. [PubMed: 15788781]
38. Ciruela F, Soloviev MM, Chan WY, McIlhinney RA. Homer-1c/vesl-1l modulates the cell surface targeting of metabotropic glutamate receptor type 1alpha: Evidence for an anchoring function. Molecular and cellular neurosciences 2000;15:36–50. [PubMed: 10662504]
39. Clapcote SJ, Lipina TV, Millar JK, Mackie S, Christie S, Ogawa F, Lerch JP, Trimble K, Uchiyama M, Sakuraba Y, Kaneda H, Shiroishi T, Houslay MD, Henkelman RM, Sled JG, Gondo Y, Porteous DJ, Roder John C. Behavioral phenotypes of disc1 missense mutations in mice. Neuron 2007;54:387–402. [PubMed: 17481393]
40. Creese, I. Stimulants: Neurochemical, behavioral, and clinical perspectives. New York: Raven; 1983.
41. Creese I, Burt DR, Snyder SH. Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. Science 1976;192:481–483. [PubMed: 3854]
42. Crestani F, Keist R, Fritschy JM, Benke D, Vogt K, Prut L, Bluthmann H, Mohler H, Rudolph U. Trace fear conditioning involves hippocampal alpha 5 gabaa receptors. Proceedings of the National Academy of Sciences 2002;99:8980–8985.
43. Csomor PA, Stadler RR, Feldon J, Yee BK, Geyer MA, Vollenweider FX. Haloperidol differentially modulates prepulse inhibition and p50 suppression in healthy humans stratified for low and high gating levels. Neuropsychopharmacology 2008;33:497–512. [PubMed: 17460616]
44. Dawson GR, Maubach KA, Collinson N, Cobain M, Everitt BJ, MacLeod AM, Choudhury HI, McDonald LM, Pillai G, Rycroft W, Smith AJ, Sternfeld F, Tattersall FD, Wafford KA, Reynolds DS, Seabrook GR, Atack JR. An inverse agonist selective for {alpha}5 subunit-containing gabaa receptors enhances cognition. J Pharmacol Exp Ther 2006;316:1335–1345. [PubMed: 16326923]
45. Doherty JM, Masten VL, Powell SB, Ralph RJ, Klamer D, Low MJ, Geyer MA. Contributions of dopamine d1, d2, and d3 receptor subtypes to the disruptive effects of cocaine on prepulse inhibition in mice. Neuropsychopharmacology 2008;33:2648–2656. [PubMed: 18075489]
46. Duffy L, Cappas E, Scimone A, Schofield PR, Karl T. Behavioral profile of a heterozygous mutant mouse model for egf-like domain neuregulin 1. Behav Neurosci 2008;122:748–759. [PubMed: 18729627]
47. Dulawa SC, Gross C, Stark KL, Hen R, Geyer MA. Knockout mice reveal opposite roles for serotonin 1a and 1b receptors in prepulse inhibition. Neuropsychopharmacology 2000;22:650–659. [PubMed: 10788764]
48. Duncan GE, Moy SS, Lieberman JA, Koller BH. Effects of haloperidol, clozapine, and quetiapine on sensorimotor gating in a genetic model of reduced nmda receptor function. Psychopharmacology (Berl) 2006;184:190–200. [PubMed: 16362405]
49. Duncan GE, Moy SS, Lieberman JA, Koller BH. Typical and atypical antipsychotic drug effects on locomotor hyperactivity and deficits in sensorimotor gating in a genetic model of nmda receptor hypofunction. Pharmacol Biochem Behav 2006;85:481–491. [PubMed: 17097724]
50. Eells JB, Lipska BK, Yeung SK, Misler JA, Nikodem VM. Nurr1-null heterozygous mice have reduced mesolimbic and mesocortical dopamine levels and increased stress-induced locomotor activity. Behav Brain Res 2002;136:267–275. [PubMed: 12385813]
51. Eells JB, Misler JA, Nikodem VM. Early postnatal isolation reduces dopamine levels, elevates dopamine turnover and specifically disrupts prepulse inhibition in nurr1-null heterozygous mice. Neuroscience 2006;140:1117–1126. [PubMed: 16690213]
52. Fernandes C, Hoyle E, Dempster E, Schalkwyk LC, Collier DA. Performance deficit of alpha7 nicotinic receptor knockout mice in a delayed matching-to-place task suggests a mild impairment of working/episodic-like memory. Genes, brain, and behavior 2006;5:433–440.
53. Foa L, Rajan I, Haas K, Wu GY, Brakeman P, Worley P, Cline H. The scaffold protein, homer1b/c, regulates axon pathfinding in the central nervous system in vivo. Nat Neurosci 2001;4:499–506. [PubMed: 11319558]

54. Fornai F, Chen K, Giorgi FS, Gesi M, Alessandri MG, Shih JC. Striatal dopamine metabolism in monoamine oxidase b-deficient mice: A brain dialysis study. J Neurochem 1999;73:2434–2440. [PubMed: 10582603]
55. Francis DD, Szegda K, Campbell G, Martin WD, Insel TR. Epigenetic sources of behavioral differences in mice. Nat Neurosci 2003;6:445–446. [PubMed: 12665797]
56. Freedman R, Adler LE, Leonard S. Alternative phenotypes for the complex genetics of schizophrenia. Biol Psychiatry 1999;45:551–558. [PubMed: 10088045]
57. Freedman R, Olincy A, Ross RG, Waldo MC, Stevens KE, Adler LE, Leonard S. The genetics of sensory gating deficits in schizophrenia. Current psychiatry reports 2003;5:155–161. [PubMed: 12685995]
58. Gainetdinov RR, Wetsel WC, Jones SR, Levin ED, Jaber M, Caron MG. Role of serotonin in the paradoxical calming effect of psychostimulants on hyperactivity. Science 1999;283:397–401. [PubMed: 9888856]
59. Gallinat J, Bajbouj M, Sander T, Schlattmann P, Xu K, Ferro EF, Goldman D, Winterer G. Association of the g1947a comt (val(108/158)met) gene polymorphism with prefrontal p300 during information processing. Biol Psychiatry 2003;54:40–48. [PubMed: 12842307]
60. Garzya V, Forbes IT, Gribble AD, Hadley MS, Lightfoot AP, Payne AH, Smith AB, Douglas SE, Cooper DG, Stansfield IG, Meeson M, Dodds EE, Jones DN, Wood M, Reavill C, Scorer CA, Worby A, Riley G, Eddershaw P, Ioannou C, Donati D, Hagan JJ, Ratti EA. Studies towards the identification of a new generation of atypical antipsychotic agents. Bioorganic & medicinal chemistry letters 2007;17:400–405. [PubMed: 17084080]
61. Gerdjikov TV, Rudolph U, Keist R, Möhler H, Feldon J, Yee BK. Hippocampal [alpha]5 subunit-containing gabaa receptors are involved in the development of the latent inhibition effect. Neurobiology of Learning and Memory 2008;89:87–94. [PubMed: 17638582]
62. Gerlai R, Pisacane P, Erickson S. Heregulin, but not erbb2 or erbb3, heterozygous mutant mice exhibit hyperactivity in multiple behavioral tasks. Behav Brain Res 2000;109:219–227. [PubMed: 10762692]
63. Geyer MA, Ellenbroek B. Animal behavior models of the mechanisms underlying antipsychotic atypicality. Prog Neuropsychopharmacol Biol Psychiatry 2003;27:1071–1079. [PubMed: 14642967]
64. 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 (Berl) 2001;156:117–154. [PubMed: 11549216]
65. Geyer, MA.; Markou, A. The role of preclinical models in the development of psychotropic drugs. In: Davis, KL.; Charney, D.; Coyle, JT.; Nemeroff, CB., editors. Neuropsychopharmacology: The fifth generation of progress. Lippincott, Williams & Wilkins; 2002. p. 445-455.
66. Geyer MA, McIlwain KL, Paylor R. Mouse genetic models for prepulse inhibition: An early review. Mol Psychiatry 2002;7:1039–1053. [PubMed: 12476318]
67. Geyer, MA.; Moghaddam, B. Animal models relevant to schizophrenia disorders. In: Charney, D.; Coyle, J.; Davis, K.; Nemeroff, CB., editors. Neuropsychopharmacology: The fifth generation of progress. Lippincott Williams & Wilkins; 2002. p. 689-701.
68. Giakoumaki SG, Bitsios P, Frangou S. The level of prepulse inhibition in healthy individuals may index cortical modulation of early information processing. Brain Res 2006;1078:168–170. [PubMed: 16492380]
69. Giakoumaki SG, Roussos P, Bitsios P. Improvement of prepulse inhibition and executive function by the comt inhibitor tolcapone depends on comt val158met polymorphism. Neuropsychopharmacology. 2008
70. 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;379:606–612. [PubMed: 8628395]
71. Goff DC, Henderson DC, Evins AE, Amico E. A placebo-controlled crossover trial of d-cycloserine added to clozapine in patients with schizophrenia. Biol Psychiatry 1999;45:512–514. [PubMed: 10071726]

72. Goff DC, Tsai G, Levitt J, Amico E, Manoach D, Schoenfeld DA, Hayden DL, McCarley R, Coyle JT. A placebo-controlled trial of d-cycloserine added to conventional neuroleptics in patients with schizophrenia. Arch Gen Psychiatry 1999;56:21–27. [PubMed: 9892252]
73. Goff DC, Tsai G, Manoach DS, Coyle JT. Dose-finding trial of d-cycloserine added to neuroleptics for negative symptoms in schizophrenia. Am J Psychiatry 1995;152:1213–1215. [PubMed: 7625475]
74. Gogos JA, Morgan M, Luine V, Santha M, Ogawa S, Pfaff D, Karayiorgou M. Catechol-o-methyltransferase-deficient mice exhibit sexually dimorphic changes in catecholamine levels and behavior. Proc Natl Acad Sci U S A 1998;95:9991–9996. [PubMed: 9707588]
75. Gogos JA, Santha M, Takacs Z, Beck KD, Luine V, Lucas LR, Nadler JV, Karayiorgou M. The gene encoding proline dehydrogenase modulates sensorimotor gating in mice. Nat Genet 1999;21:434–439. [PubMed: 10192398]
76. Golimbet V, Gritsenko I, Alfimova M, Lebedeva I, Lezheiko T, Abramova L, Kaleda V, Ebstein R. Association study of comt gene val158met polymorphism with auditory p300 and performance on neurocognitive tests in patients with schizophrenia and their relatives. World J Biol Psychiatry 2006;7:238–245. [PubMed: 17071544]
77. Golub MS, Germann SL, Lloyd KC. Behavioral characteristics of a nervous system-specific erbb4 knock-out mouse. Behav Brain Res 2004;153:159–170. [PubMed: 15219717]
78. Gothelf D, Schaer M, Eliez S. Genes, brain development and psychiatric phenotypes in velo-cardio-facial syndrome. Developmental disabilities research reviews 2008;14:59–68. [PubMed: 18636637]
79. Gottesman, II. Schizophrenia genesis. New York: W.H. Freeman; 1991.
80. Gould TD, Gottesman II. Psychiatric endophenotypes and the development of valid animal models. Genes, brain, and behavior 2006;5:113–119.
81. Gouzoulis-Mayfrank E, Habermeyer E, Hermle L, Steinmeyer AM, Kunert HJ, Sass H. Hallucinogenic drug induced states resemble acute endogenous psychoses: Results of an empirical study. European Psychiatry 1998;13:399–406. [PubMed: 19698655]
82. Gray L, van den Buuse M, Scarr E, Dean B, Hannan AJ. Clozapine reverses schizophrenia-related behaviours in the metabotropic glutamate receptor 5 knockout mouse: Association with n-methyl-d-aspartic acid receptor up-regulation. Int J Neuropsychopharmacol 2008:1–16.
83. Green MF, Butler PD, Chen Y, Geyer MA, Silverstein S, Wynn JK, Yoon JH, Zemon V. Perception measurement in clinical trials of schizophrenia: Promising paradigms from cntrics. Schizophr Bull 2009;35:163–181. [PubMed: 19023123]
84. Greenwood TA, Braff DL, Light GA, Cadenhead KS, Calkins ME, Dobie DJ, Freedman R, Green MF, Gur RE, Gur RC, Mintz J, Nuechterlein KH, Olincy A, Radant AD, Seidman LJ, Siever LJ, Silverman JM, Stone WS, Swerdlow NR, Tsuang DW, Tsuang MT, Turetsky BI, Schork NJ. Initial heritability analyses of endophenotypic measures for schizophrenia: The consortium on the genetics of schizophrenia. Arch Gen Psychiatry 2007;64:1242–1250. [PubMed: 17984393]
85. Harrison PJ, Law AJ. Neuregulin 1 and schizophrenia: Genetics, gene expression, and neurobiology. Biol Psychiatry 2006;60:132–140. [PubMed: 16442083]
86. Harrison PJ, Owen MJ. Genes for schizophrenia? Recent findings and their pathophysiological implications. Lancet 2003;361:417–419. [PubMed: 12573388]
87. Harrison PJ, Weinberger DR. Schizophrenia genes, gene expression, and neuropathology: On the matter of their convergence. Mol Psychiatry 2005;10:40–68. [PubMed: 15263907]image 45
88. Harte MK, Powell SB, Swerdlow NR, Geyer MA, Reynolds GP. Deficits in parvalbumin and calbindin immunoreactive cells in the hippocampus of isolation reared rats. Journal of Neural Transmission 2007;114:893–898. [PubMed: 17594127]
89. Hauser J, Rudolph U, Keist R, Mohler H, Feldon J, Yee BK. Hippocampal [alpha]5 subunit-containing gabaa receptors modulate the expression of prepulse inhibition. Mol Psychiatry 2004;10:201–207. [PubMed: 15263904]
90. Hazlett EA, Buchsbaum MS. Sensorimotor gating deficits and hypofrontality in schizophrenia. Front Biosci 2001;6:D1069–1072. [PubMed: 11532605]
91. Hazlett EA, Buchsbaum MS, Haznedar MM, Singer MB, Germans MK, Schnur DB, Jimenez EA, Buchsbaum BR, Troyer BT. Prefrontal cortex glucose metabolism and startle eyeblink modification abnormalities in unmedicated schizophrenia patients. Psychophysiology 1998;35:186–198. [PubMed: 9529945]

92. Heldt SA, Green A, Ressler KJ. Prepulse inhibition deficits in gad65 knockout mice and the effect of antipsychotic treatment. Neuropsychopharmacology 2004;29:1610–1619. [PubMed: 15114343]

93. Hennah W, Tuulio-Henriksson A, Paunio T, Ekelund J, Varilo T, Partonen T, Cannon TD, Lonnqvist J, Peltonen L. A haplotype within the disc1 gene is associated with visual memory functions in families with a high density of schizophrenia. Mol Psychiatry 2005;10:1097–1103. [PubMed: 16103888]

94. Hikida T, Jaaro-Peled H, Seshadri S, Oishi K, Hookway C, Kong S, Wu D, Xue R, Andrade M, Tankou S, Mori S, Gallagher M, Ishizuka K, Pletnikov M, Kida S, Sawa A. Dominant-negative disc1 transgenic mice display schizophrenia-associated phenotypes detected by measures translatable to humans. Proc Natl Acad Sci U S A 2007;104:14501–14506. [PubMed: 17675407]

95. Hitzemann R, Malmanger B, Belknap J, Darakjian P, McWeeney S. Short-term selective breeding for high and low prepulse inhibition of the acoustic startle response; pharmacological characterization and qtl mapping in the selected lines. Pharmacology Biochemistry and Behavior 2008;90:525–533.

96. Hoffman HS, Ison JR. Reflex modification in the domain of startle: I. Some empirical findings and their implications for how the nervous system processes sensory input. Psychological review 1980;87:175–189. [PubMed: 7375610]

97. Jaubert PJ, Golub MS, Lo YY, Germann SL, Dehoff MH, Worley PF, Kang SH, Schwarz MK, Seeburg PH, Berman RF. Complex, multimodal behavioral profile of the homer1 knockout mouse. Genes, brain, and behavior 2007;6:141–154.

98. Javitt DC. Glutamate as a therapeutic target in psychiatric disorders. Mol Psychiatry 2004;9:984–997. [PubMed: 15278097]

99. Javitt DC, Balla A, Sershen H, Lajtha AAE. Bennett research award. Reversal of phencyclidine-induced effects by glycine and glycine transport inhibitors. Biol Psychiatry 1999;45:668–679. [PubMed: 10187996]

100. Javitt DC, Sershen H, Hashim A, Lajtha A. Inhibition of striatal dopamine release by glycine and glycyldodecylamide. Brain Res Bull 2000;52:213–216. [PubMed: 10822163]

101. Javitt DC, Zukin SR. Recent advances in the phencyclidine model of schizophrenia. Am J Psychiatry 1991;148:1301–1308. [PubMed: 1654746]

102. Johnson JW, Ascher P. Glycine potentiates the nmda response in cultured mouse brain neurons. Nature 1987;325:529–531. [PubMed: 2433595]

103. Jones, DNC.; Gartlon, JE.; Minassian, A.; Perry, W.; Geyer, MA. Developing new drugs for schizophrenia: From animals to the clinic. In: McArthur, R.; Borsini, R., editors. Animal and translational models for cns drug discovery: Psychiatric disorders. New York: Elsevier; 2008. p. 199-262.

104. Joober R, Zarate JM, Rouleau GA, Skamene E, Boksa P. Provisional mapping of quantitative trait loci modulating the acoustic startle response and prepulse inhibition of acoustic startle. Neuropsychopharmacology 2002;27:765–781. [PubMed: 12431851]

105. Jurata LW, Gallagher P, Lemire AL, Charles V, Brockman JA, Illingworth EL, Altar CA. Altered expression of hippocampal dentate granule neuron genes in a mouse model of human 22q11 deletion syndrome. Schizophr Res 2006;88:251–259. [PubMed: 17008057]

106. Kanahara N, Shimizu E, Ohgake S, Fujita Y, Kohno M, Hashimoto T, Matsuzawa D, Shirayama Y, Hashimoto K, Iyo M. Glycine and d: -serine, but not d: -cycloserine, attenuate prepulse inhibition deficits induced by nmda receptor antagonist mk-801. Psychopharmacology (Berl) 2008;198:363–374. [PubMed: 18437299]

107. Karayiorgou M, Morris MA, Morrow B, Shprintzen RJ, Goldberg R, Borrow J, Gos A, Nestadt G, Wolyniec PS, Lasseter VK, et al. Schizophrenia susceptibility associated with interstitial deletions of chromosome 22q11. Proc Natl Acad Sci U S A 1995;92:7612–7616. [PubMed: 7644464]

108. Karl T, Duffy L, Scimone A, Harvey RP, Schofield PR. Altered motor activity, exploration and anxiety in heterozygous neuregulin 1 mutant mice: Implications for understanding schizophrenia. Genes, brain, and behavior 2007;6:677–687.

109. Karper LP, Freeman GK, Grillon C, Morgan CA 3rd, Charney DS, Krystal JH. Preliminary evidence of an association between sensorimotor gating and distractibility in psychosis. The Journal of neuropsychiatry and clinical neurosciences 1996;8:60–66. [PubMed: 8845703]

110. Koike H, Arguello PA, Kvajo M, Karayiorgou M, Gogos JA. Disc1 is mutated in the 129s6/svev strain and modulates working memory in mice. Proceedings of the National Academy of Sciences 2006;103:3693–3697.
111. Kopin IJ. Catecholamine metabolism: Basic aspects and clinical significance. Pharmacol Rev 1985;37:333–364. [PubMed: 3915090]
112. Krebs-Thomson K, Ruiz EM, Masten V, Buell M, Geyer MA. The roles of 5-ht1a and 5-ht2 receptors in the effects of 5-meo-dmt on locomotor activity and prepulse inhibition in rats. Psychopharmacology (Berl) 2006;189:319–329. [PubMed: 17013638]
113. Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, Heninger GR, Bowers MB Jr, Charney DS. Subanesthetic effects of the noncompetitive nmda antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry 1994;51:199–214. [PubMed: 8122957]
114. Kumari V, Fannon D, Geyer MA, Premkumar P, Antonova E, Simmons A, Kuipers E. Cortical grey matter volume and sensorimotor gating in schizophrenia. Cortex; a journal devoted to the study of the nervous system and behavior 2008;44:1206–1214. [PubMed: 18761134]
115. Kumari V, Gray JA, Geyer MA, ffytche D, Soni W, Mitterschiffthaler MT, Vythelingum GN, Simmons A, Williams SC, Sharma T. Neural correlates of tactile prepulse inhibition: A functional mri study in normal and schizophrenic subjects. Psychiatry research 2003;122:99–113. [PubMed: 12714174]
116. Kvajo M, McKellar H, Arguello PA, Drew LJ, Moore H, MacDermott AB, Karayiorgou M, Gogos JA. A mutation in mouse disc1 that models a schizophrenia risk allele leads to specific alterations in neuronal architecture and cognition. Proc Natl Acad Sci U S A 2008;105:7076–7081. [PubMed: 18458327]
117. Lachman HM, Papolos DF, Saito T, Yu YM, Szumlanski CL, Weinshilboum RM. Human catechol-o-methyltransferase pharmacogenetics: Description of a functional polymorphism and its potential application to neuropsychiatric disorders. Pharmacogenetics 1996;6:243–250. [PubMed: 8807664]
118. Le Pen G, Kew J, Alberati D, Borroni E, Heitz MP, Moreau JL. Prepulse inhibition deficits of the startle reflex in neonatal ventral hippocampal-lesioned rats: Reversal by glycine and a glycine transporter inhibitor. Biol Psychiatry 2003;54:1162–1170. [PubMed: 14643083]
119. Leonard S, Gault J, Hopkins J, Logel J, Vianzon R, Short M, Drebing C, Berger R, Venn D, Sirota P, Zerbe G, Olincy A, Ross RG, Adler LE, Freedman R. Association of promoter variants in the alpha7 nicotinic acetylcholine receptor subunit gene with an inhibitory deficit found in schizophrenia. Arch Gen Psychiatry 2002;59:1085–1096. [PubMed: 12470124]
120. Lewis DA, Volk DW, Hashimoto T. Selective alterations in prefrontal cortical gaba neurotransmission in schizophrenia: A novel target for the treatment of working memory dysfunction. Psychopharmacology (Berl) 2004;174:143–150. [PubMed: 15205885]
121. Li W, Zhou Y, Jentsch JD, Brown RA, Tian X, Ehninger D, Hennah W, Peltonen L, Lonnqvist J, Huttunen MO, Kaprio J, Trachtenberg JT, Silva AJ, Cannon TD. Specific developmental disruption of disrupted-in-schizophrenia-1 function results in schizophrenia-related phenotypes in mice. Proc Natl Acad Sci U S A 2007;104:18280–18285. [PubMed: 17984054]
122. 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 (Berl) 2005;179:54–67. [PubMed: 15759151]
123. Lipina T, Weiss K, Roder J. The ampakine cx546 restores the prepulse inhibition and latent inhibition deficits in mglur5-deficient mice. Neuropsychopharmacology 2007;32:745–756. [PubMed: 16936708]
124. Liu H, Abecasis GR, Heath SC, Knowles A, Demars S, Chen YJ, Roos JL, Rapoport JL, Gogos JA, Karayiorgou M. Genetic variation in the 22q11 locus and susceptibility to schizophrenia. Proc Natl Acad Sci U S A 2002;99:16859–16864. [PubMed: 12477929]
125. Lominac KD, Oleson EB, Pava M, Klugmann M, Schwarz MK, Seeburg PH, During MJ, Worley PF, Kalivas PW, Szumlinski KK. Distinct roles for different homer1 isoforms in behaviors and associated prefrontal cortex function. J Neurosci 2005;25:11586–11594. [PubMed: 16354916]
126. Low NC, Hardy J. What is a schizophrenic mouse? Neuron 2007;54:348–349. [PubMed: 17481386]

127. Lu BY, Martin KE, Edgar JC, Smith AK, Lewis SF, Escamilla MA, Miller GA, Canive JM. Effect of catechol o-methyltransferase val(158)met polymorphism on the p50 gating endophenotype in schizophrenia. Biol Psychiatry 2007;62:822–825. [PubMed: 17448448]
128. Ludewig K, Geyer MA, Vollenweider FX. Deficits in prepulse inhibition and habituation in never-medicated, first-episode schizophrenia. Biol Psychiatry 2003;54:121–128. [PubMed: 12873801]
129. Ludewig S, Ludewig K, Geyer MA, Hell D, Vollenweider FX. Prepulse inhibition deficits in patients with panic disorder. Depress Anxiety 2002;15:55–60. [PubMed: 11891993]
130. Mackeprang T, Kristiansen KT, Glenthoj BY. Effects of antipsychotics on prepulse inhibition of the startle response in drug-naive schizophrenic patients. Biol Psychiatry 2002;52:863–873. [PubMed: 12399139]
131. Mackie S, Millar JK, Porteous DJ. Role of disc1 in neural development and schizophrenia. Current Opinion in Neurobiology 2007;17:95–102. [PubMed: 17258902]
132. Malhotra AK, Adler CM, Kennison SD, Elman I, Pickar D, Breier A. Clozapine blunts n-methyl-d-aspartate antagonist-induced psychosis: A study with ketamine. Biol Psychiatry 1997;42:664–668. [PubMed: 9325559]
133. Malhotra AK, Pinals DA, Adler CM, Elman I, Clifton A, Pickar D, Breier A. Ketamine-induced exacerbation of psychotic symptoms and cognitive impairment in neuroleptic-free schizophrenics. Neuropsychopharmacology 1997;17:141–150. [PubMed: 9272481]
134. Martin LF, Kem WR, Freedman R. Alpha-7 nicotinic receptor agonists: Potential new candidates for the treatment of schizophrenia. Psychopharmacology (Berl) 2004;174:54–64. [PubMed: 15205879]
135. Martin LF, Leonard S, Hall MH, Tregellas JR, Freedman R, Olincy A. Sensory gating and alpha-7 nicotinic receptor gene allelic variants in schizoaffective disorder, bipolar type. Am J Med Genet B Neuropsychiatr Genet 2007;144B:611–614. [PubMed: 17192894]
136. McBain CJ, Mayer ML. N-methyl-d-aspartic acid receptor structure and function. Physiological reviews 1994;74:723–760. [PubMed: 8036251]
137. McOmish CE, Burrows E, Howard M, Scarr E, Kim D, Shin HS, Dean B, van den Buuse M, Hannan AJ. Phospholipase c-beta1 knockout mice exhibit endophenotypes modeling schizophrenia which are rescued by environmental enrichment and clozapine administration. Mol Psychiatry 2008;13:661–672. [PubMed: 17667964]
138. Mei L, Xiong WC. Neuregulin 1 in neural development, synaptic plasticity and schizophrenia. Nat Rev Neurosci 2008;9:437–452. [PubMed: 18478032]
139. Meincke U, Morth D, Voss T, Thelen B, Geyer MA, Gouzoulis-Mayfrank E. Prepulse inhibition of the acoustically evoked startle reflex in patients with an acute schizophrenic psychosis--a longitudinal study. Eur Arch Psychiatry Clin Neurosci 2004;254:415–421. [PubMed: 15538598]
140. Meyer U, Feldon J, Schedlowski M, Yee BK. Towards an immuno-precipitated neurodevelopmental animal model of schizophrenia. Neuroscience and biobehavioral reviews 2005;29:913–947. [PubMed: 15964075]
141. Möhler H. Molecular regulation of cognitive functions and developmental plasticity: Impact of $GABA_A$ receptors. Journal of Neurochemistry 2007;102:1–12.
142. Moy SS, Perez A, Koller BH, Duncan GE. Amphetamine-induced disruption of prepulse inhibition in mice with reduced nmda receptor function. Brain Res 2006;1089:186–194. [PubMed: 16638606]
143. O'Tuathaigh CM, Babovic D, O'Meara G, Clifford JJ, Croke DT, Waddington JL. Susceptibility genes for schizophrenia: Characterisation of mutant mouse models at the level of phenotypic behaviour. Neuroscience and biobehavioral reviews 2007;31:60–78. [PubMed: 16782199]
144. O'Tuathaigh CM, Babovic D, O'Sullivan GJ, Clifford JJ, Tighe O, Croke DT, Harvey R, Waddington JL. Phenotypic characterization of spatial cognition and social behavior in mice with 'knockout' of the schizophrenia risk gene neuregulin 1. Neuroscience 2007;147:18–27. [PubMed: 17512671]
145. Oranje B, Geyer MA, Bocker KB, Leon Kenemans J, Verbaten MN. Prepulse inhibition and p50 suppression: Commonalities and dissociations. Psychiatry research 2006;143:147–158. [PubMed: 16879870]

146. Oranje B, Gispen-de Wied CC, Verbaten MN, Kahn RS. Modulating sensory gating in healthy volunteers: The effects of ketamine and haloperidol. Biol Psychiatry 2002;52:887–895. [PubMed: 12399142]

147. Papaleo F, Crawley JN, Song J, Lipska BK, Pickel J, Weinberger DR, Chen J. Genetic dissection of the role of catechol-o-methyltransferase in cognition and stress reactivity in mice. J Neurosci 2008;28:8709–8723. [PubMed: 18753372]

148. Paterlini M, Zakharenko SS, Lai WS, Qin J, Zhang H, Mukai J, Westphal KG, Olivier B, Sulzer D, Pavlidis P, Siegelbaum SA, Karayiorgou M, Gogos JA. Transcriptional and behavioral interaction between 22q11.2 orthologs modulates schizophrenia-related phenotypes in mice. Nat Neurosci 2005;8:1586–1594. [PubMed: 16234811]

149. Paylor R, Crawley JN. Inbred strain differences in prepulse inhibition of the mouse startle response. Psychopharmacology 1997;132:169–180. [PubMed: 9266614]

150. Paylor, R.; Nguyen, M.; Crawley, JN.; Patrick, J.; Beaudet, A.; Orr-Urtreger, A. Learning & memory. Vol. 5. Cold Spring Harbor; N.Y: 1998. Alpha7 nicotinic receptor subunits are not necessary for hippocampal-dependent learning or sensorimotor gating: A behavioral characterization of acra7-deficient mice; p. 302-316.

151. Perry W, Braff DL. Information-processing deficits and thought disorder in schizophrenia. Am J Psychiatry 1994;151:363–367. [PubMed: 8109644]

152. Perry W, Geyer MA, Braff DL. Sensorimotor gating and thought disturbance measured in close temporal proximity in schizophrenic patients. Arch Gen Psychiatry 1999;56:277–281. [PubMed: 10078506]

153. Perry W, Minassian A, Feifel D, Braff DL. Sensorimotor gating deficits in bipolar disorder patients with acute psychotic mania. Biol Psychiatry 2001;50:418–424. [PubMed: 11566158]

154. Perry W, Minassian A, Lopez B, Maron L, Lincoln A. Sensorimotor gating deficits in adults with autism. Biol Psychiatry. 2006

155. Pletnikov MV, Ayhan Y, Nikolskaia O, Xu Y, Ovanesov MV, Huang H, Mori S, Moran TH, Ross CA. Inducible expression of mutant human disc1 in mice is associated with brain and behavioral abnormalities reminiscent of schizophrenia. Mol Psychiatry 2007;13:173–186. [PubMed: 17848917]

156. Porteous DJ, Millar JK. Disrupted in schizophrenia 1: Building brains and memories. Trends in Molecular Medicine 2006;12:255–261. [PubMed: 16679065]

157. Porteous DJ, Thomson P, Brandon NJ, Millar JK. The genetics and biology of disc1--an emerging role in psychosis and cognition. Biological Psychiatry 2006;60:123–131. [PubMed: 16843095]

158. Postma P, Gray JA, Sharma T, Geyer M, Mehrotra R, Das M, Zachariah E, Hines M, Williams SC, Kumari V. A behavioural and functional neuroimaging investigation into the effects of nicotine on sensorimotor gating in healthy subjects and persons with schizophrenia. Psychopharmacology (Berl) 2006;184:589–599. [PubMed: 16456657]

159. Powell SB, Risbrough VB, Lehmann-Masten V, Krebs-Thomson K, Hen R, Gingrich JA, Geyer MA. The indoleamine hallucinogens, psilocin and 5meodmt, increase prepulse inhibition in mice: Role of 5-ht1a and 5-ht2a receptors. Society for Neuroscience, New Orleans, LA, 2003 Abstract Viewer/Itinerary Planner, 2003, Program No. 315.7.

160. Powell SB, Young JW, Ong JC, Caron MG, Geyer MA. Atypical antipsychotics clozapine and quetiapine attenuate prepulse inhibition deficits in dopamine transporter knockout mice. Behav Pharmacol 2008;19:562–565. [PubMed: 18690110]

161. Quednow BB, Wagner M, Mossner R, Maier W, Kuhn K-U. Sensorimotor gating of schizophrenia patients depends on catechol o-methyltransferase val158met polymorphism. Schizophr Bull 2008:sbn088.

162. Ralph-Williams RJ, Lehmann-Masten V, Geyer MA. Dopamine d1 rather than d2 receptor agonists disrupt prepulse inhibition of startle in mice. Neuropsychopharmacology 2003;28:108–118. [PubMed: 12496946]

163. Ralph RJ, Caine SB. Dopamine d1 and d2 agonist effects on prepulse inhibition and locomotion: Comparison of sprague-dawley rats to swiss-webster, 129x1/svj, c57bl/6j, and dba/2j mice. J Pharmacol Exp Ther 2005;312:733–741. [PubMed: 15494551]

164. Ralph RJ, Paulus MP, Fumagalli F, Caron MG, Geyer MA. Prepulse inhibition deficits and perseverative motor patterns in dopamine transporter knock-out mice: Differential effects of d1 and d2 receptor antagonists. J Neurosci 2001;21:305–313. [PubMed: 11150348]

165. Ralph RJ, Varty GB, Kelly MA, Wang YM, Caron MG, Rubinstein M, Grandy DK, Low MJ, Geyer MA. 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;19:4627–4633. [PubMed: 10341260]

166. Reynolds GP, Abdul-Monim Z, Neill JC, Zhang ZJ. Calcium binding protein markers of gaba deficits in schizophrenia--postmortem studies and animal models. Neurotox Res 2004;6:57–61. [PubMed: 15184106]

167. Reynolds GP, Czudek C, Andrews HB. Deficit and hemispheric asymmetry of gaba uptake sites in the hippocampus in schizophrenia. Biol Psychiatry 1990;27:1038–1044. [PubMed: 2159350]

168. Rimer M, Barrett DW, Maldonado MA, Vock VM, Gonzalez-Lima F. Neuregulin-1 immunoglobulin-like domain mutant mice: Clozapine sensitivity and impaired latent inhibition. Neuroreport 2005;16:271–275. [PubMed: 15706234]

169. Roth BL, Sheffler DJ, Kroeze WK. Magic shotguns versus magic bullets: Selectively non-selective drugs for mood disorders and schizophrenia. Nat Rev Drug Discov 2004;3:353–359. [PubMed: 15060530]

170. Roussos P, Giakoumaki SG, Rogdaki M, Pavlakis S, Frangou S, Bitsios P. Prepulse inhibition of the startle reflex depends on the catechol o-methyltransferase val158met gene polymorphism. Psychol Med 2008:1–8. [PubMed: 19079825]

171. Rudolph U, Möhler H. Gaba-based therapeutic approaches: Gabaa receptor subtype functions. Current Opinion in Pharmacology 2006;6:18–23. [PubMed: 16376150]

172. Savonenko AV, Melnikova T, Laird FM, Stewart KA, Price DL, Wong PC. Alteration of bace1-dependent nrg1/erbb4 signaling and schizophrenia-like phenotypes in bace1-null mice. Proceedings of the National Academy of Sciences 2008;105:5585–5590.

173. Schwabe K, Freudenberg F, Koch M. Selective breeding of reduced sensorimotor gating in wistar rats. Behavior Genetics 2007;37:706–712. [PubMed: 17899353]

174. Seeman P, Lee T. Antipsychotic drugs: Direct correlation between clinical potency and presynaptic action on dopamine neurons. Science 1975;188:1217–1219. [PubMed: 1145194]

175. Segal, DS.; Geyer, MA.; Schuckit, A. Stimulant-induced psychosis: An evaluation of animal models. In: Youdim, MBH.; Lovenberg, W.; Sharman, DF.; Lagnado, JR., editors. Essays in neurochemistry and neuropharmacology. New York: John Wiley & Sons; 1981. p. 95-130.

176. Sesack SR, Hawrylak VA, Matus C, Guido MA, Levey AI. Dopamine axon varicosities in the prelimbic division of the rat prefrontal cortex exhibit sparse immunoreactivity for the dopamine transporter. J Neurosci 1998;18:2697–2708. [PubMed: 9502827]

177. Shen S, Lang B, Nakamoto C, Zhang F, Pu J, Kuan S-L, Chatzi C, He S, Mackie I, Brandon NJ, Marquis KL, Day M, Hurko O, McCaig CD, Riedel G, St Clair D. Schizophrenia-related neural and behavioral phenotypes in transgenic mice expressing truncated disc1. J Neurosci 2008;28:10893–10904. [PubMed: 18945897]

178. Shi L, Fatemi SH, Sidwell RW, Patterson PH. Maternal influenza infection causes marked behavioral and pharmacological changes in the offspring. J Neurosci 2003;23:297–302. [PubMed: 12514227]

179. Shilling PD, Saint Marie RL, Shoemaker JM, Swerdlow NR. Strain differences in the gating-disruptive effects of apomorphine: Relationship to gene expression in nucleus accumbens signaling pathways. Biological Psychiatry 2008;63:748–758. [PubMed: 18083141]

180. Sipes TA, Geyer MA. 8-oh-dpat disruption of prepulse inhibition in rats: Reversal with (+)way 100,135 and localization of site of action. Psychopharmacology (Berl) 1995;117:41–48. [PubMed: 7724701]

181. Smith SEP, Li J, Garbett K, Mirnics K, Patterson PH. Maternal immune activation alters fetal brain development through interleukin-6. J Neurosci 2007;27:10695–10702. [PubMed: 17913903]

182. Spielewoy C, Biala G, Roubert C, Hamon M, Betancur C, Giros B. Hypolocomotor effects of acute and daily d-amphetamine in mice lacking the dopamine transporter. Psychopharmacology (Berl) 2001;159:2–9. [PubMed: 11797063]

183. Spooren W, Mombereau C, Maco M, Gill R, Kemp JA, Ozmen L, Nakanishi S, Higgins GA. Pharmacological and genetic evidence indicates that combined inhibition of nr2a and nr2b subunit

containing nmda receptors is required to disrupt prepulse inhibition. Psychopharmacology (Berl) 2004;175:99–105. [PubMed: 14985927]

184. Stefanis NC, Van Os J, Avramopoulos D, Smyrnis N, Evdokimidis I, Hantoumi I, Stefanis CN. Variation in catechol-o-methyltransferase val158 met genotype associated with schizotypy but not cognition: A population study in 543 young men. Biol Psychiatry 2004;56:510–515. [PubMed: 15450787]
185. Stefansson H, Petursson H, Sigurdsson E, Steinthorsdottir V, Bjornsdottir S, Sigmundsson T, Ghosh S, Brynjolfsson J, Gunnarsdottir S, Ivarsson O, Chou TT, Hjaltason O, Birgisdottir B, Jonsson H, Gudnadottir VG, Gudmundsdottir E, Bjornsson A, Ingvarsson B, Ingason A, Sigfusson S, Hardardottir H, Harvey RP, Lai D, Zhou M, Brunner D, Mutel V, Gonzalo A, Lemke G, Sainz J, Johannesson G, Andresson T, Gudbjartsson D, Manolescu A, Frigge ML, Gurney ME, Kong A, Gulcher JR, Stefansson K. Neuregulin 1 and susceptibility to schizophrenia. The American Journal of Human Genetics 2002;71:877–892.
186. Sternfeld F, Carling RW, Jelley RA, Ladduwahetty T, Merchant KJ, Moore KW, Reeve AJ, Street LJ, O'Connor D, Sohal B, Atack JR, Cook S, Seabrook G, Wafford K, Tattersall FD, Collinson N, Dawson GR, Castro JL, MacLeod AM. Selective, orally active γ-aminobutyric acida α5 receptor inverse agonists as cognition enhancers. J Med Chem 2004;47:2176–2179. [PubMed: 15084116]
187. Straub RE, Weinberger DR. Schizophrenia genes - famine to feast. Biol Psychiatry 2006;60:81–83. [PubMed: 16843093]
188. Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a complex trait: Evidence from a meta-analysis of twin studies. Arch Gen Psychiatry 2003;60:1187–1192. [PubMed: 14662550]
189. Swerdlow NR, Benbow CH, Zisook S, Geyer MA, Braff DL. A preliminary assessment of sensorimotor gating in patients with obsessive compulsive disorder. Biol Psychiatry 1993;33:298–301. [PubMed: 8471686]
190. Swerdlow NR, Geyer MA, Braff DL. Neural circuit regulation of prepulse inhibition of startle in the rat: Current knowledge and future challenges. Psychopharmacology (Berl) 2001;156:194–215. [PubMed: 11549223]
191. Swerdlow NR, Geyer MA, Shoemaker JM, Light GA, Braff DL, Stevens KE, Sharp R, Breier M, Neary A, Auerbach PP. Convergence and divergence in the neurochemical regulation of prepulse inhibition of startle and n40 suppression in rats. Neuropsychopharmacology 2006;31:506–515. [PubMed: 16123772]
192. Swerdlow NR, Karban B, Ploum Y, Sharp R, Geyer MA, Eastvold A. Tactile prepuff inhibition of startle in children with tourette's syndrome: In search of an "Fmri-friendly" Startle paradigm. Biol Psychiatry 2001;50:578–585. [PubMed: 11690592]
193. Swerdlow NR, Light GA, Cadenhead KS, Sprock J, Hsieh MH, Braff DL. Startle gating deficits in a large cohort of patients with schizophrenia: Relationship to medications, symptoms, neurocognition, and level of function. Arch Gen Psychiatry 2006;63:1325–1335. [PubMed: 17146007]
194. Swerdlow NR, Martinez ZA, Hanlon FM, Platten A, Farid M, Auerbach P, Braff DL, Geyer MA. Toward understanding the biology of a complex phenotype: Rat strain and substrain differences in the sensorimotor gating-disruptive effects of dopamine agonists. J Neurosci 2000;20:4325–4336. [PubMed: 10818168]
195. Swerdlow NR, Paulsen J, Braff DL, Butters N, Geyer MA, Swenson MR. Impaired prepulse inhibition of acoustic and tactile startle response in patients with huntington's disease. J Neurol Neurosurg Psychiatry 1995;58:192–200. [PubMed: 7876851]
196. Swerdlow NR, Shoemaker JM, Platten A, Pitcher L, Goins J, Auerbach PP. Heritable differences in the dopaminergic regulation of sensorimotor gating. I. Apomorphine effects on startle gating in albino and hooded outbred rat strains and their f1 and n2 progeny. Psychopharmacology (Berl) 2004;174:441–451. [PubMed: 15300358]
197. Swerdlow NR, Weber M, Qu Y, Light GA, Braff DL. Realistic expectations of prepulse inhibition in translational models for schizophrenia research. Psychopharmacology (Berl) 2008;199:331–388. [PubMed: 18568339]
198. Szumlinski KK, Lominac KD, Kleschen MJ, Oleson EB, Dehoff MH, Schwarz MK, Seeburg PH, Worley PF, Kalivas PW. Behavioral and neurochemical phenotyping of homer1 mutant mice: Possible relevance to schizophrenia. Genes, brain, and behavior 2005;4:273–288.

199. Takeuchi T, Kiyama Y, Nakamura K, Tsujita M, Matsuda I, Mori H, Munemoto Y, Kuriyama H, Natsume R, Sakimura K, Mishina M. Roles of the glutamate receptor epsilon2 and delta2 subunits in the potentiation and prepulse inhibition of the acoustic startle reflex. The European journal of neuroscience 2001;14:153–160. [PubMed: 11488959]

200. Thaker GK. Schizophrenia endophenotypes as treatment targets. Expert opinion on therapeutic targets 2007;11:1189–1206. [PubMed: 17845145]

201. Torkamanzehi A, Boksa P, Joober R. Prepulse inhibition (ppi) of tactile startle response in recombinant congenic strains of mice: Qtl mapping and comparison with acoustic ppi. Journal of Genetics and Genomics 2008;35:139–151. [PubMed: 18355757]

202. Tsai G, Ralph-Williams RJ, Martina M, Bergeron R, Berger-Sweeney J, Dunham KS, Jiang Z, Caine SB, Coyle JT. Gene knockout of glycine transporter 1: Characterization of the behavioral phenotype. Proceedings of the National Academy of Sciences 2004;101:8485–8490.

203. Tsai G, Yang P, Chung LC, Lange N, Coyle JT. D-serine added to antipsychotics for the treatment of schizophrenia. Biol Psychiatry 1998;44:1081–1089. [PubMed: 9836012]

204. Tunbridge EM, Harrison PJ, Weinberger DR. Catechol-o-methyltransferase, cognition, and psychosis: Val158met and beyond. Biological Psychiatry 2006;60:141–151. [PubMed: 16476412]

205. Turetsky BI, Calkins ME, Light GA, Olincy A, Radant AD, Swerdlow NR. Neurophysiological endophenotypes of schizophrenia: The viability of selected candidate measures. Schizophr Bull 2007;33:69–94. [PubMed: 17135482]

206. van Berckel BN, Evenblij CN, van Loon BJ, Maas MF, van der Geld MA, Wynne HJ, van Ree JM, Kahn RS. D-cycloserine increases positive symptoms in chronic schizophrenic patients when administered in addition to antipsychotics: A double-blind, parallel, placebo-controlled study. Neuropsychopharmacology 1999;21:203–210. [PubMed: 10432468]

207. van Berckel BN, Oranje B, van Ree JM, Verbaten MN, Kahn RS. The effects of low dose ketamine on sensory gating, neuroendocrine secretion and behavior in healthy human subjects. Psychopharmacology (Berl) 1998;137:271–281. [PubMed: 9683005]

208. Weber M, Chang WL, Breier M, Ko D, Swerdlow NR. Heritable strain differences in sensitivity to the startle gating-disruptive effects of d2 but not d3 receptor stimulation. Behav Pharmacol 2008;19:786–795. [PubMed: 19020413]

209. Xiao B, Tu JC, Worley PF. Homer: A link between neural activity and glutamate receptor function. Curr Opin Neurobiol 2000;10:370–374. [PubMed: 10851183]

210. Yamashita M, Fukushima S, Shen HW, Hall FS, Uhl GR, Numachi Y, Kobayashi H, Sora I. Norepinephrine transporter blockade can normalize the prepulse inhibition deficits found in dopamine transporter knockout mice. Neuropsychopharmacology 2006;31:2132–2139. [PubMed: 16407898]

211. Yavich L, Forsberg MM, Karayiorgou M, Gogos JA, Mannisto PT. Site-specific role of catechol-o-methyltransferase in dopamine overflow within prefrontal cortex and dorsal striatum. J Neurosci 2007;27:10196–10209. [PubMed: 17881525]

212. Yee BHJ, Dolgov VV, Keist R, Möhler H, Rudolph U, Feldon J. Gaba receptors containing the alpha5 subunit mediate the trace effect in aversive and appetitive conditioning and extinction of conditioned fear. The European journal of neuroscience 2004;20:14. [PubMed: 15245475]

213. Yee BK, Keist R, von Boehmer L, Studer R, Benke D, Hagenbuch N, Dong Y, Malenka RC, Fritschy JM, Bluethmann H, Feldon J, Mohler H, Rudolph U. A schizophrenia-related sensorimotor deficit links alpha 3-containing gabaa receptors to a dopamine hyperfunction. Proc Natl Acad Sci U S A 2005;102:17154–17159. [PubMed: 16284244]

214. Young JW, Crawford N, Kelly JS, Kerr LE, Marston HM, Spratt C, Finlayson K, Sharkey J. Impaired attention is central to the cognitive deficits observed in alpha 7 deficient mice. Eur Neuropsychopharmacol. 2006

215. Young JW, Powell SB, Risbrough V, Marston HM, Geyer MA. Using the matrics to guide development of a preclinical cognitive test battery for research in schizophrenia. Pharmacology & Therapeutics. In Press, Corrected Proof

216. Zhang Z, Sun J, Reynolds GP. A selective reduction in the relative density of parvalbumin-immunoreactive neurons in the hippocampus in schizophrenia patients. Chinese medical journal 2002;115:819–823. [PubMed: 12123544]

217. Zhou X, Geyer MA, Kelsoe JR. Does disrupted-in-schizophrenia (disc1) generate fusion transcripts? Mol Psychiatry 2008;13:361–363. [PubMed: 18347596]

218. Zhou X, Long JM, Geyer MA, Masliah E, Kelsoe JR, Wynshaw-Boris A, Chien KR. Reduced expression of the sp4 gene in mice causes deficits in sensorimotor gating and memory associated with hippocampal vacuolization. Mol Psychiatry 2004;10:393–406. [PubMed: 15558077]

219. Zhou X, Tang W, Greenwood TA, Guo S, He3 L, Geyer MA, Kelsoe JR. Transcription factor sp4 is a susceptibility gene for bipolar disorder. PlosOne. 2009In Press