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Genetic Models of Sensorimotor Gating: Relevance to Neuropsychiatric Disorders

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Abstract

Sensorimotor gating, or the ability of a sensory event to suppress a motor response, can be measured operationally via prepulse inhibition (PPI) of the startle response. PPI is deficient in schizophrenia patients as well as other neuropsychiatric disorders, can be measured across species, and has been used widely as a translational tool in preclinical neuropharmacological and genetic research. First developed to assess drug effects in pharmacological and developmental models, PPI has become one of the standard behavioral measures in genetic models of schizophrenia and other neuropsychiatric disorders that exhibit PPI deficits. In this chapter we review the literature on genetic models of sensorimotor gating and discuss the utility of PPI as a tool in phenotyping mutant mouse models. We highlight the approaches to genetic mouse models of neuropsychiatric disease, discuss some of the important caveats to these approaches, and provide a comprehensive table covering the more recent genetic models that have evaluated PPI.

Keywords

Prepulse inhibition; Startle; Mouse models; Schizophrenia; Genetic; Mutant

1 Introduction: Definitions and Measures of Sensorimotor Gating

Sensorimotor gating refers to the regulation of sensory information as it is transmitted to motor output systems. When sensory information is processed centrally, it requires some degree of filtering or “gating” prior to accessing and impinging upon motor output. While this process has long been observed at multiple levels of biology, the synaptic and cellular mechanism of sensorimotor gating (Frost et al. 2003; Nusbaum and Contreras 2004; Rose and Scott 2003) as well as the functional implications (Braff 2010, 2011; Swerdlow et al.

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2008) are starting to be elucidated. One form of sensorimotor gating that is widely studied in humans and animals is prepulse inhibition (PPI) of startle. PPI is a form of startle plasticity in which presentation of a weak stimulus (prepulse) preceding an intense startling stimulus (pulse) by 30–500 ms inhibits the startle response (Graham 1975; Hoffman and Ison 1980). The fundamental mechanism underlying this inhibition is thought to resemble the normal process of filtering incoming sensory stimuli (Geyer and Braff 1987). PPI levels may indicate the current integrity of sensorimotor gating mechanisms, providing an operational measure of sensorimotor gating. In humans, startle is measured from the eye blink response through electromyographic recordings of the orbicularis oculi muscle (Fridlund and Cacioppo 1986) and typically involves startle to acoustic stimuli, although tactile stimuli have been used as well (Braff et al. 1992; Kumari et al. 2003; Neuner et al. 2010; Swerdlow et al. 2001b). PPI deficits are observed in schizophrenia patients [for review see (Braff et al. 2001; Swerdlow et al. 2008)], their unaffected first degree relatives (Cadenhead et al. 2000), and patients with schizotypal personality disorder (Cadenhead et al. 1993). Additionally, several other neuropsychiatric disorders are associated with decreased PPI, including Obsessive–Compulsive Disorder (Swerdlow et al. 1993), Tourette's syndrome (Swerdlow et al. 2001b), Huntington's disease (Swerdlow et al. 1995), manic bipolar patients (Perry et al. 2001), Panic Disorder (Ludewig et al. 2002), Fragile X syndrome (Frankland et al. 2004; Hessl et al. 2009), and adults with autism (Perry et al. 2007). Although the core symptoms of these disorders are diverse, a feature common to all of them is deficient gating, with a gating deficit predominating in the cognitive sphere in some disorders and in the sensory or motor domains in others. Thus, deficient gating has been reported across a variety of neuropsychiatric disorders, with PPI deficits in schizophrenia patients being the best characterized and the most widely replicated (Braff et al. 2001; Kumari et al. 2008; Ludewig et al. 2003; Mackeprang et al. 2002; Swerdlow et al. 2008).

Sensorimotor gating abnormalities, as measured by PPI, are being used as an endophenotype in genetic studies of schizophrenia (Braff et al. 2007; Greenwood et al. 2011), and meet the criteria outlined for a viable endophenotype (Turetsky et al. 2007). With an increased focus on observable and measurable behaviors as rational approaches to genetic studies of heterogeneous neuropsychiatric diseases such as schizophrenia (Gottesman and Gould 2003), large-scale genetic studies are examining neurophysiological measures such as PPI, P50 auditory evoked suppression, antisaccade eye movement, mismatch negativity, and P300 event-related potential (Turetsky et al. 2007). Recent studies suggest that PPI is heritable (Hasenkamp et al. 2010) and associated with polymorphisms in the CHRNA3 gene (Petrovsky et al. 2010), neuregulin 1 (Roussos et al. 2011), and COMT (Giakoumaki et al. 2008; Quednow et al. 2008; Roussos et al. 2008). The use of PPI as an endophenotype in genetic studies of schizophrenia, combined with the observation that PPI has a strong genetic component in mice (Francis et al. 2003), indicates that PPI may be a useful behavioral phenotype to consider in genetic mouse models related to neuropsychiatric disease, particularly schizophrenia. While there are certainly many other symptoms, behavioral traits, and neurophysiological deficits observed across the heterogeneous group of patients with schizophrenia, PPI appears to be a viable endophenotype for human genetic studies and thus a reasonable approach to investigate in genetic animal models. Additionally, considering that PPI measures a fundamental component of information processing and is observable across many species, it is a useful endpoint with which to understand the more general impact of specific genes on neurobehavioral function and on the neural substrates underlying this function.

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 an overview of PPI in genetic mouse models, concentrating on the time period since the Swerdlow et al. (2008) review. We

discuss the contribution and usefulness of PPI as a phenotype in the context of genetic mouse models and speculate about the significance of PPI deficits and future directions for the field. There have been previous reviews on candidate genes for schizophrenia (Arguello and Gogos 2010; O'Tuathaigh et al. 2007), and reviews focusing specifically on PPI, which summarized studies of strain differences, genetic mutants, and the pharmacology of PPI in mice (Geyer et al. 2002; Powell et al. 2009; Swerdlow et al. 2008). In this review, we highlight the approaches to genetic mouse models of neuropsychiatric disease, discuss some of the important caveats to these approaches, and provide a comprehensive table covering the genetic models that have evaluated PPI since the Swerdlow et al. (2008) review. To that end, we discuss PPI as a phenotype in genetic mouse models generated to address hypotheses regarding the pathophysiology of neuropsychiatric disease, candidate genes, and basic proteins involved in neural development or synaptic function. 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 and/or neuropsychiatric disease [i.e. hypothesis-generating; or phenotype-genotype approaches (Jacobson and Cryan 2010)].

2 Utility of Prepulse Inhibition Measures in Genetic Models of Schizophrenia

Mutant mouse models of neuropsychiatric disease have targeted genes involved in the pathophysiology of the disease, candidate or susceptibility genes thought to be involved in the etiology of the disease, or genes involved in basic physiological processes. Because many of the target genes overlap at the functional level across different disorders (e.g. proteins involved in basic processes of neurodevelopment), manipulation of these genes may have relevance to many neuropsychiatric disorders. Thus, it is important to determine the relevant behavioral tests to best understand the underlying brain abnormalities resulting from genetic alterations of proteins. Second, it is critical to develop animal models to screen novel therapeutics for specific domains of function. In this context, PPI has emerged as a useful behavior with which to assess the integrity of basic neural circuits in genetic mouse models and to screen for pharmacological agents, particularly in the context of identifying treatments for schizophrenia.

2.1 Relationship of PPI to Psychiatric Symptoms, Neurocognitive Measures, and Overall Function

Attempts to relate PPI deficits to the positive, negative, and cognitive symptoms of schizophrenia have yielded mixed results (Thaker 2007). PPI negatively correlates with thought disorder (Meincke et al. 2004; Perry and Braff 1994; Perry et al. 1999) and distractibility (Karper et al. 1996) in schizophrenia. PPI increases S. B. Powell et al. observed with risperidone treatment correlated with improvements in PANSS general psychopathology subscale scores (Martinez-Gras et al. 2009) in schizophrenia patients. In a well-powered study with over 300 subjects, PPI did not correlate with cognitive measures using traditional "pen and paper" tests [i.e. Wisconsin card sorting task (WCST), California verbal learning task, etc.], but did correlate positively with global assessment of function (GAF) and Independent Living scales (Swerdlow et al. 2006). There have been some studies demonstrating a relationship between cognitive constructs and PPI levels. 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 (Bitsios et al. 2006; Csomor et al. 2008; Giakoumaki et al. 2006), a finding that should be examined further in patient populations. The cognitive neuroscience treatment research to improve cognition in Schizophrenia (CNTRICS) 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 (Green et al. 2009). 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. For the purpose of evaluating genetic mouse models of neuropsychiatric disease, 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. The approach of using endophenotypes in genetic studies has greatly strengthened the ability to conduct cross-species translational studies by providing specific observables for study in experimental animals [reviewed in (Geyer and Markou 2002; Gould and Gottesman 2006) Waddington, chapter in this book]. Useful endophenotypes in this context are measures that are observed in humans and can be measured in animals.

2.2 PPI as an Indicator of Neural Processes and a Pharmacological Screen

A PPI deficit in a genetic mutant could indicate that the gene may be involved in the neural circuitry known to modulate PPI [e.g. cortical, limbic, striatal (Swerdlow et al. 2001a)]; in other words it could function as a "surrogate measure for neural processes" as Swerdlow et al. (2008) suggest. 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. Additionally, mutant mouse models offer the opportunity to screen putative antipsychotics that may involve a novel target and avoid the problems of receptor tautology inherent in many pharmacological studies [e.g. dopamine agonist-induced disruption blocked by a dopamine antagonist; as discussed in Powell et al. (2009). Using mutant mice to screen for putative antipsychotics may provide a means to develop novel drug targets not achieved with current pharmacological disruptions of PPI (see Table 1 for examples).

2.3 PPI as a Tool to Evaluate Gene–Environment Interactions

Studies of gene–environment interactions may be particularly informative for neuropsychiatric diseases, most of which likely involve a genetic susceptibility combined with environmental factors (e.g. stress) to observe the full manifestation of the disease (Gottesman 1991) (see also Sen and Karg, Gross and Carola chapters in this book). 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 physiological 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. There are a few examples in which PPI has been a useful endpoint with which to assess gene–environment interactions in mouse models. For example, PPI deficits associated with maternal immune activation (MIA) with PolyI:C during mid-gestation, which typically leads to deficits in PPI in adult offspring (Meyer et al. 2005; Shi et al. 2003), are blocked in interleukin (IL)-6 KO dams (Smith et al. 2007). Thus, PPI in a genetic mutant (IL-6 KO mice) was used to determine the mechanism for the effects of an environmental manipulation (immune activation) on brain development. An example of a PPI phenotype being "rescued" in a KO mouse comes from studies in Phospholipase C –β 1 KO mice, in which PPI deficits and locomotor hyperactivity were attenuated in KO mice by environmental enrichment or clozapine (McOmish et al. 2008) (Table 1). More recently, and perhaps most important to etiological models of neuropsychiatric disease, there have been several studies examining the "two-hit" approach (Eells et al. 2006; Ibi et al. 2010). For example, nuclear receptor null Nurr1 heterozygous mice, which display reduced mesocortical and mesolimbic dopamine (Eells et al. 2002), showed reduced PPI after postnatal isolation rearing, an effect that was not observed with

either isolation rearing or genotype alone (Eells et al. 2006). 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.

2.4 Evaluating the Role of a Susceptibility Gene in Pathology

When evaluating the role of a susceptibility gene implicated in any neuropsychiatric disease, 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 the given neuropsychiatric condition under study (e.g. schizophrenia). Using schizophrenia as an example, the 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 (e.g. deficient social interaction, disruptions in attentional set shifting). The lack of a PPI deficit in this case does not indicate that the genetic model is not of relevance to schizophrenia. There are several examples provided in Table 1 in which a PPI deficit was not present in a mutant mouse but other behavioral differences such as deficits in memory, social interaction, or set shifting were apparent in the mice. The likelihood of being able to reproduce 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 (see Jones et al. (2008); Powell et al. (2009) for discussion). For that matter, it is not the case that all aspects of schizophrenia are observed in each patient carrying the diagnosis. Rather, support for a model should be based on the convergence of data from multiple sources [e.g. many animal models, human genetic studies, etc. (Jones et al. 2008)]. Thus, no one phenotype should be considered as being either necessary or sufficient to support a model for a neuropsychiatric disease, particularly since the distributions of the behavioral measure often overlap between healthy volunteers and patients, as is the case with PPI and schizophrenia (Swerdlow et al. 2008). Thus an animal model should not be rejected based on "normal" PPI. For example, GLAST KO mice lacking the glutamate and aspartate transporter do not show any deficits in PPI but do show deficits in social approach, nest building, and pairwise discrimination learning (Karlsson et al. 2009). 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 disease and no such association is found. As we have argued previously, 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 a specific disease, e.g. schizophrenia (Powell et al. 2009). Interestingly, there are a few examples where KO or transgenic mice actually had increased PPI relative to wild-type controls. One such example is the FMR1 KO mice (Paylor et al. 2008; Thomas et al. 2011a, b; but see de Vrij et al. 2008; Table 2). It remains unclear how such findings should be interpreted, but the possibility that the loss of the gene may lead to gain of function should be considered.

2.5 Methodological Considerations with Specific Relevance to Genetic Models of Sensorimotor Gating

For a detailed description of the methods of acoustic startle and PPI in mice see Geyer and Dulawa (2003). When conducting an initial analysis of startle and PPI in a genetic mutant, several considerations should be made when evaluating PPI. Typically, startle sessions involve variable prepulse intensities (e.g. 3, 6, 12 dB above background), which should produce an incremental increase in PPI with increasing prepulse intensities. 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 Geyer et al. (2002). In a study examining strain differences in hearing and PPI, Willot et al. (1994) showed a relationship between PPI levels and hearing impairments. Hearing loss is also exacerbated by age, particularly in specific strains of mice such as C57s, which experience high frequency hearing loss with age (Willott et al. 1994). One way to avoid relying solely on auditory processing is to assess multimodal PPI using light as a prepulse and/or airpuffs as a startling stimulus (Brody et al. 2004; Young et al. 2010). This multisensory approach can avoid potential confounds of hearing loss and still enable the evaluation of PPI. It should be noted, however, that some degree of noise is often produced with the delivery of airpuff stimuli, therefore, data on airpuff-tactile startle should be interpreted with this consideration in mind. Other tactile stimuli, such as mild footshock could provide an alternative approach to this issue. Another way to provide a gross measure of hearing in genetic mutants is to incorporate a "startle threshold" block into the session, in which increasing decibels of acoustic stimuli are presented to measure startle magnitude across these intensities (Brody et al. 2004). The threshold at which the mouse begins to startle can then be evaluated. Additionally, differences in baseline startle magnitude can confound effects on PPI. Although dissociations between startle and PPI have been reported in mice (Brody et al. 2004) and rats (Sipes and Geyer 1994), large differences in baseline startle magnitude can complicate interpretations of changes in PPI. If large differences in baseline startle are observed, startle magnitude can be "matched" either by using a range of startle stimuli (e.g. 110, 120 dB) paired with the prepulse stimuli or doing a post hoc analysis of only those animals across genotypes that have comparable levels of startle. We have included results on startle magnitude [pulse alone (PA)] in Tables 1–5 when the data were provided and indicated studies that did not report data on startle magnitude. A good example of testing over a wide range of startle amplitudes can be found in Savonenko et al. (2009) in their studies of EP2 KO mice. The background strain on which genetic mutants are made should be considered as well. For a discussion of the issue surrounding background strain the reader is referred to Crawley (2007) and Geyer et al. (2002).

3 Approaches to Genetic Models of Sensorimotor Gating

3.1 Overview of Molecular Genetic Techniques

Broadly defined, behavioral genetic approaches can be divided into two main approaches either beginning with the gene of interest or the behavior of interest (Jacobson and Cryan 2010). Gene-based or "reverse genetics" approaches begin with the targeted gene being manipulated in the animal and the resultant behavior evaluated. Phenotype-based or "forward genetics" approaches begin with the targeted behavioral phenotype (trait) and then involve subsequent genetic analysis of the trait. Most genetic studies of sensorimotor gating have focused on genebased approaches, and as such, these approaches are discussed in more detail than phenotype-based approaches, which are discussed more extensively in Tarantino and Eisener-Doman (2011). The goals for any genetic approach can be very different—some approaches seek to understand the more global role of a specific gene in a particular phenotype related to a disease, while others may be designed to elucidate the role of a particular gene in a cellular process, in neural circuit abnormalities, or in brain development. Studies representing all of these goals are well represented in the literature on genetic models of sensorimotor gating (see Tables 1–5). The techniques used to generate molecular genetic models using the gene-based (reverse genetic) approach include constitutive gene deletion (knockout), insertion of exogenous DNA into the genome (transgenic), and insertion of gene at a particular locus via homologous recombination (knockin) [reviewed in (Crawley 2007; Tecott and Wehner 2001)]. Conditional genetic manipulations, which restrict the expression of a targeted gene either temporally or regionally, are useful in avoiding complications of in utero lethality or compensatory brain changes, or when specific hypotheses exist regarding the developmental expression of a gene or the specific

neuroanatomical function of the gene. Examples of conditional genetic manipulations include the Cre-LoxP system in which the targeted gene is floxed with lox-p sites. When combined with Cre recombinase, the floxed gene is expressed, giving regional, cell-specific, or temporal control over expression or deletion of targeted gene (van der Neut 1997; Wang 2009). Restriction to specific brain regions can be achieved through the use of specific promoters used to drive expression. For example, the CaMKIIα promoter restricts expression of a genetic mutation to the forebrain (Mayford et al. 1996). Additional examples of tools to achieve temporal control over gene function involve the Tet-On and Tet-Off systems. With these systems, the target gene is linked to either the tetracycline-controlled transactivator (tTA) or the reverse tTA (rtTA) and can be either turned "on" with doxycycline administered (tTA; Tet-On) or turned "off" in the presence of doxycycline (rtTA; Tet-Off) (Mansuy and Bujard 2000). Thus, by combining some of these approaches, conditional and inducible gene expression in mouse brain can be achieved. Additionally, insertion of large segments of DNA into the genome can be achieved through the use of bacterial artificial chromosomes (BAC transgenics) (Heintz 2001). The BAC transgenic technique is a useful approach when a large segment of DNA has been implicated in a disease (e.g. 22q11.2 microdeletion or microduplications). For example, BAC transgenic technology was used to generate two lines of transgenic mice expressing different genes located on the 22q11.2 segment of the chromosome. Interestingly, mice overexpressing Prodh and Vpreb2 showed increased PPI, while mice overexpressing Zdhhc8, Ranbp1, Htf9c, T10, Arvcf, COMT showed no differences in PPI (Stark et al. 2009). More recent techniques, such as in utero gene transfer, are being developed to modulate the expression of genes during specific stages of embryonic development (Niwa et al. 2010).

"Phenotype-based" approaches to behavioral genetics include "forward genetic screens" such as mutagenesis via radiation or chemical means [e.g. ENU mutagenesis; (Tarantino and Bucan 2000) and quantitative trait loci (QTL) studies on crosses of inbred mouse strains with distinct phenotypes or on mice or rats selectively bred for PPI levels (Hitzemann et al. 2008; Tarantino and Eisener-Doman 2011). Thus far, most of the PPI mutants identified through ENU mutagenesis screens have had some amount of hearing loss, and thus the specificity of the PPI "phenotype" was most likely confounded by deafness (Lisa Tarantino, personal communication). Other molecular genetic tools such as siRNA, in which double stranded RNA homologous to the targeted gene is made and then inserted into the cell to block expression of that gene, and viral transfection, in which genes are inserted into viral vectors and injected into the nucleus of cells, are additional techniques used in neuroscience research assessing sensorimotor gating, but will not be discussed in this chapter. Due to the increasingly large number of genetic models generated in which PPI was evaluated, we will provide some examples in the text of different genetic approaches undertaken to study sensorimotor gating, but the reader is referred to Tables 1–5 for a comprehensive review of the recent genetic models assessing PPI.

3.2 Models Based on Hypotheses Regarding the Pathophysiology of Disease

Genetic models of sensorimotor gating deficits were based initially on the hypothesized pathophysiology of schizophrenia or the known mechanism of action of both antipsychotic and psychotomimetic drugs [e.g. amphetamine, PCP]. Thus, early genetic mutants focused primarily on dopamine (Ralph et al. 2001) and glutamate (Brody and Geyer 2004; Duncan et al. 2004) neurotransmitters and receptors (e.g. dopamine-related genes, glutamate-related genes). Many of these observed effects [e.g. PPI deficits in dopamine transporter KO mice (Ralph et al. 2001)] were not surprising based on the extensive pharmacology of PPI deficits in rodents, but nevertheless the genetic models provided proof of concept that constitutive gene deletion could produce dramatic functional effects on sensorimotor gating in adult animals. PPI deficits in dopamine transporter knockout mice strengthened the converging

evidence that dopamine hyperfunction played an important role in sensorimotor gating and potentially the pathophysiology of schizophrenia. Similarly, PPI deficits in metabotropic glutamate mutants (Brody et al. 2003; Brody and Geyer 2004; Gray et al. 2009; Kinney et al. 2003) have stimulated interest in these receptors as targets for drug development (Cleva and Olive 2011). Genetic approaches to pathophysiology of neuropsychiatric disease are becoming increasingly sophisticated and many of these models incorporate assessments of PPI as a relevant behavioral phenotype (Tables 3, 4). Jumping off from the original observation that N-methyl-D-aspartate (NMDA) NR1 hypomorphs show PPI deficits in addition to other behavioral abnormalities (Duncan et al. 2004), several genetic mutants have been made based on reduced NMDA receptor expression, including NMDA subtype-specific mutants (reviewed in Powell et al. (2009)) and downstream signaling proteins (Table 3).

The converging GABA-glutamate theory of schizophrenia stems from two lines of evidence (Coyle 2004). First, the glutamate hypothesis of schizophrenia is derived from evidence that acute administration of phencyclidine (PCP), a noncompetitive NMDA antagonist, produces schizophrenia-like symptoms in healthy humans (Javitt 2004; Javitt and Zukin 1991). Extending such observations, several experimental studies have utilized another NMDA antagonist, ketamine, to induce a model psychosis in normal volunteers (Abel et al. 2003; Krystal et al. 1994; Oranje et al. 2002; van Berckel et al. 1998) and to exacerbate symptoms in patients with schizophrenia (Malhotra et al. 1997a, b; Krystal et al. 1994, 2003). Additionally, studies on postmortem brain tissue from schizophrenia patients show altered GABAergic interneuron function, particularly in parvalbumin (PV) interneurons (Benes and Berretta 2001; Lewis et al. 2005). Evidence that NMDA hypofunction specifically on GABA interneurons plays a role in the pathogenesis of schizophrenia comes from several lines of preclinical research. First, NMDA antagonists increase the firing rate of pyramidal cells and increase prefrontal glutamate release (Jackson et al. 2004; Moghaddam et al. 1997), suggesting that NMDA antagonists are preferentially blocking inhibitory interneurons. Second, preclinical studies suggest that GABA interneurons are more sensitive to NMDA antagonists than other neuronal subtypes such as pyramidal neurons (Grunze et al. 1996). Third, repeated exposure to NMDA antagonists such as ketamine decreases PV and GAD67 expression (Behrens et al. 2007). Based on these converging lines of evidence, Belforte et al. (2010) used the Cre-LoxP system to engineer mice with deletion of NR1 specifically in GABAergic interneurons (Table 1). Their elegant set of studies showed that reduction in NR1 early in postnatal development produced deficits in PPI, but that adult NR1 reduction had no effect on PPI. These studies corroborate previous studies reporting PPI deficits with constitutive NR1 reduction throughout the brain (Duncan et al. 2004). There have been several other genetic mutants created to test hypotheses regarding glutamate signaling (see Table 4). For example, mice with pre-adolescent forebrain-specific deletions of the vesicular glutamate transporter VGLUT2$^{f/f;CKII/Cre}$ show PPI deficits, which are attenuated with the antipsychotic drug aripiprazole (Wallén-Mackenzie et al. 2009). Genetic mutants of specific proteins involved in NMDA receptor signaling such as mice heterozygous for SynGAP gene deletion also show PPI deficits in addition to other behavioral abnormalities (Guo et al. 2009). For a review of other neurotransmitter-related genetic mutants [e.g. acetylcholine, serotonin, dopamine (see Table 4)].

In addition to classic neurotransmitters, the important role of neuropeptides in neuropsychiatric disease is becoming more widely appreciated. PPI has been assessed in genetic mutants for many neuropeptides including angiotensin, neurotensin, corticotropin releasing factor (CRF) overexpression, oxytocin, arginine vasopressin, neuropeptide Y, PACAP, and Relaxin-3 (Table 4). Stress physiology, particularly CRF and glucocorticoids, has been implicated in neuropsychiatric disease. Mice overexpressing a CRF transgene exhibit deficits in PPI (at low prepulse intensities), which are normalized by CRF1

antagonists, whereas glucocorticoid receptor antagonists did not reverse the PPI deficit (Groenink et al. 2008). Moreover, several genetic mutants have been created to determine the role of specific proteins in brain processes, including second messenger signaling, synaptic proteins, synaptic vesicles, protein kinases, etc. (Table 3). While the direct link for many of these proteins has not necessarily been established for specific neuropsychiatric diseases, a thorough behavioral evaluation of these mice including an assessment of PPI can help elucidate the functional implications of the target protein. For example, gene deletion of PDE4B, which catalyzes the degradation of cAMP and is widely expressed in brain, is associated with PPI deficits (Siuciak et al. 2008). Decreased presynaptic proteins such as synaptophysin, SNAP-25, and complexin II have been observed in postmortem brains of schizophrenia patients (Harrison and Weinberger 2005). These data, combined with evidence of problems with neuronal migration and abnormal neuronal processes, have led investigators to conceptualize schizophrenia as a disease of functional “dysconnectivity” (Friston and Frith 1995; McGlashan and Hoffman 2000; Weinberger et al. 1992) or a “disorder of the synapse” (Frankle et al. 2003; Mirnics et al. 2001) reviewed in (Harrison and Weinberger 2005). Thus many genetic mutants have been created for specific synaptic proteins (Table 3). For example, SYNII, a vesicle-linked phosphoprotein that plays a role in neuronal development and neurotransmitter release (Cesca et al. 2010), is genetically associated with schizophrenia, decreased in brain of schizophrenia patients, and increased with chronic antipsychotic drug treatment (Chen et al. 2004; Chong et al. 2002). SYNII KO mice exhibit decreased PPI, providing more evidence for the essential role of SYNII in synaptic function and behavior (Dyck et al. 2007, 2009). Similarly, a mutation of SNAP-25, a SNARE protein that is integral to synaptic function and neurotransmitter release, is associated with PPI deficits (Oliver and Davies 2009).

3.3 Genetic Mouse Models as Pharmacological Tools

Because many of the early molecular genetic approaches focused on neurotransmitter receptor genes, several of these mutants have also been used to delineate the receptor mechanisms of drugs that disrupt PPI in order to expand our understanding of the neurotransmitter systems and neural circuitry underlying deficient PPI (Doherty et al. 2008; Dulawa et al. 1997; Ralph et al. 1999; van den Buuse et al. 2011a) (Table 4). Since most of these genetic mutants were built on rat pharmacology, we must keep in mind several important species differences between the pharmacology of mouse versus rat PPI (e.g. differential effects of dopamine D1 and D2 receptors, 5-HT agonists, etc.; Powell et al. 2009). 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 (Swerdlow et al. 2008). 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. Nevertheless, drugs that both impair and improve PPI continue to be investigated in genetic mutants. This approach is particularly useful in determining the functional role of a receptor (e.g. does the gene deletion alter the response to a psychotomimetic drug) and in determining the receptor mechanisms for a drug effect when either receptor-selective drugs are not available or when novel drugs are being evaluated. For example, amphetamine disrupts PPI in WT mice, but not in mice with gene deletions of DDO, an enzyme that degrades D-aspartate (Errico et al. 2008), suggesting a functional role of DDO in PPI disruptions. Interestingly, oxytocin KO mice show an increased sensitivity to the PPI-disruptive effects of PCP (Caldwell et al. 2009), suggesting that endogenous oxytocin may protect against PCP-induced disruptions of PPI, a finding that supports the clinical data showing putative antipsychotic properties of oxytocin (Feifel et al. 2010a). A similar approach was used to show protective properties of nNOS, which synthesizes NO from L-arginine, against PPI-induced disruptions with the dopamine D1 agonist SKF81297 (Tanda et al. 2009).

3.4 Genetic Models of Candidate Genes for Neuropsychiatric Diseases

As the field of neuropsychiatric genetics has grown, several gene targets have been identified consistently for particular disorders and have thus been modified in mouse models through gene deletion, the addition of a transgene, etc. When evaluating candidate genes for mouse models, one should consider that many single nucleotide polymorphisms (SNPs) identified in genetic screens for neuropsychiatric disease 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 (Low and Hardy 2007). Table 1 summarizes genetic mouse models of vulnerability genes for schizophrenia, and Table 2 summarizes genetic models of other neuropsychiatric disorders in which PPI deficits have been observed. Two approaches in human studies have increased our understanding of the genetics of sensorimotor gating (1) assessing the relationship between polymorphisms in a target gene (e.g. NRG1, COMT) and PPI levels in healthy volunteers and (2) endophenotype-based genetic studies of schizophrenia (e.g. Consortium on the Genetics of Schizophrenia; COGS). For example, recent studies suggest that PPI is associated with polymorphisms in CHRNA3 (Petrovsky et al. 2010), neuregulin 1 (Roussos et al. 2011), and COMT (Giakoumaki et al. 2008; Quednow et al. 2008; Roussos et al. 2008) genes. Some of these same genes (e.g. NRG1, COMT) are also associated with prepulse inhibition in the COGS data set (Greenwood et al. 2011).

Several different mutants for neuregulin 1 isoforms have been created with varying effects on behavior and neuroanatomy (reviewed in Duffy et al. 2008; O'Tuathaigh et al. 2007). Overall, the PPI phenotype in NRG1 mutants has been inconsistent (O'Tuathaigh et al. 2011, 2009). The Type III NRG1 heterozygote mouse has shown abnormalities in multiple neuroanatomical and behavioral endpoints relevant to schizophrenia, including PPI deficits that are improved with chronic nicotine administration (Chen et al. 2008). CNS-specific ERBB2/B4 KO mice exhibit PPI deficits, which are attenuated by the antipsychotic drug clozapine (Barros et al. 2009). Conditional knockouts with better temporal and regional specificity have allowed for evaluation of more specific roles of NRG1 and its receptors. For example, deletion of ErbB4 selectively in PV interneurons produces PPI deficits, suggesting a functional interaction between NRG1 and the integrity of PV interneurons (Wen et al. 2010).

The COMT Val allele is associated with reduced P300 and P50 ERPs (Gallinat et al. 2003; Golimbet et al. 2006; Lu et al. 2007) and reduced PPI (Quednow et al. 2008; Roussos et al. 2008), presumably due to decreased dopamine function in the prefrontal cortex. There have been several mice created to examine the effects of COMT gene on schizophrenia relevant phenotypes, COMT KO mice (Gogos et al. 1998; Papaleo et al. 2008; Yavich et al. 2007), COMT Tg mice that overexpress the human COMT-Val polymorphism (Papaleo et al. 2008), and S-COMT isoform KO (Tammimäki et al. 2010) Thus far, none of the COMT mouse models have shown robust deficits in PPI (Table 1), although other behaviors probing prefrontal cortex such as the attentional set shifting task (ASST) are altered in the COMT-Val TG mice (Papaleo et al. 2008).

The disrupted in Schizophrenia 1 (DISC1) gene has shown association with schizophrenia and behavioral and neuroanatomical biomarkers for schizophrenia (for review see Mackie et al. 2007; Porteous et al. 2006). DISC1 is associated with schizophrenia neuropathology (Cannon et al. 2005; Callicott et al. 2005), abnormal P300 ERP (Blackwood et al. 2001), and neurocognitive function (e.g. learning and memory; Burdick et al. 2005; Cannon et al. 2005; Hennah et al. 2005). The data on the dominant negative DISC1 models have reported both decreased PPI (Hikida et al. 2007) and no change in PPI (Ibi et al. 2010); whereas, the DISC1L100P mutations have shown more consistent decreases in PPI (Lipina et al. 2011;

Lipina et al. 2010). The new technology of in utero gene transfer, allows for the knockdown of DISC1 into the mouse brain during early embryonic development. Mice with in utero knockdown of DISC1 show reduced PPI when tested in adulthood (Niwa et al. 2010). As we have discussed previously, modeling the human DISC1 mutation in mice is difficult because most of the models have assumed that the mutation in neuropsychiatric disease is due to the formation of a truncated DISC1 protein (Powell et al. 2009). Another gene, Boymaw, is also disrupted on chromosome 11 in the Scottish family. Two fusion transcripts are generated between DISC1 and Boymaw genes in the translocation carriers in the Scottish schizophrenia family (Zhou et al. 2008). Thus, expressing the two fusion transcripts may be a better strategy for creating mutant DISC1 mice for the study of neuropsychiatric disorders. The increasing identification of copy number variants (CNVs) associated with schizophrenia and large-scale GWAS studies identifying novel candidate genes will lead to even greater potential to create new mouse models (see Tables for examples). Additionally, PPI is being used more widely to characterize mutant mouse models of candidate genes for other neuropsychiatric disorders such as autism and Huntington's Disease (Table 2).

3.5 Phenotype-Based Models Revealing the Function of Genes

PPI deficits have also been used in phenotype-to-genotype approaches, or "forward genetic" screens such as ENU mutagenesis, QTL on strain crosses, and QTL with selective breeding. For example, using F2 mice from a C57BL/6 × C3h/HE cross, QTL identified 6 loci for PPI, including the gene FABP7, which has been linked to NMDA receptor function (Watanabe et al. 2007). In a study comparing A/J, C57Bl6/J, and congenic crosses thereof (recombinant congenic mouse strains) (Torkamanzehi et al. 2008) found some common markers for startle but not PPI compared to previous studies (Joober et al. 2002). Selective breeding for high and low levels of PPI has identified QTLs on chromosomes 11 and 16 in low PPI versus high PPI mouse lines (Hitzemann et al. 2008; Schwabe et al. 2007). An ENU mutagenesis screen produced 2 PPI mutants (Cook et al. 2007). One major problem with these approaches is that many of the PPI mutants, particularly with ENU mutagenesis, will likely be deaf or have some degree of hearing loss. In the (Torkamanzehi et al. 2008) study on crosses of A/J, C57Bl6/J and congenic crosses, light prepulses and tactile startle pulses were used to measure PPI to avoid this potential confound (but airpuff startle also has an acoustic component to it).

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. Phenotypic characterization of mice with mutations of genes heretofore not known to be relevant to CNS disease (some examples found in Tables 1–5) may reveal novel genes for further study of neuropsychiatric genetics. Although these approaches were gene-based, some have the capacity to identify novel genes for a particular disease, which is why we have included these examples here. Two examples of the way a novel gene of relevance to psychiatric conditions can be discovered through the creation of a mutant mouse are the SP4 and the SREB2 genes. SP4 is a member of the Sp1 family of transcription factors. 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 (Zhou et al. 2004). These studies revealed a novel Sp4 pathway that is important for hippocampal development and essential to many behaviors, including PPI, relevant to schizophrenia (Zhou et al. 2004). Zhou et al. (2009) 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. This work represents an example in which a PPI phenotype, in combination with other behavioral abnormalities, suggested the association of this gene with neuropsychiatric disorders. A

similar finding was also observed with SREB2 Tg mice, which display PPI deficits. Follow-up genetic studies in schizophrenia found a genetic association between SREB2 and schizophrenia (Matsumoto et al. 2008).

4 Discussion

Mutant mouse models of schizophrenia provide a unique way to assess the function of a susceptibility gene, test hypotheses about the pathophysiology of disease, address receptor mechanisms of drugs, and generate hypotheses about the function of relatively unknown genes. In this review, we provided a comprehensive overview of PPI deficits in genetic models since July, 2007 and elaborate on specific examples where appropriate. As illustrated in Tables 1–5, perhaps the most notable advances in genetic approaches to sensorimotor gating over the last few years have come from candidate genes for schizophrenia and other neuropsychiatric diseases exhibiting PPI deficits, genes involved in basic synaptic processes and receptor signaling, and conditional genetic approaches that help in understanding the dynamic function of specific genes both regionally and temporally. In particular, since our last reviews (Powell et al. 2009; Swerdlow et al. 2008), many genetic mutants of proteins involved in synaptic plasticity, second messenger systems, calcium signaling, etc. have been developed. In this case, PPI is used as a functional measure of sensorimotor processing in models of basic brain development. Whether or not these cellular processes turn out to be relevant for a specific disease such as schizophrenia remains to be determined. Thus far, most models are still in the “characterization” phase—testing multiple behavioral/cognitive constructs that are deficient across neuropsychiatric disorders (e.g. sensorimotor gating, attention, social interaction, learning, and memory, etc.). Few models, however, have shown any predictive power for drug development. Perhaps this new wave of mutants based on susceptibility genes, synaptic function, or brain development, as opposed to genetic manipulation based on mechanism of action of antipsychotics or psychotomimetics, will be better models to lead the field forward in medication development for mental illness. As Moore (2010) argues, too many models that are not based on either “etiologic or pathogenic” theories, may result in too many “false positives” in drug screens. Rather, refined models that more closely mimic the etiological risk factors and/or neuropathology of disease (e.g. schizophrenia) may generate more predictive models for drug development (Moore 2010). While this approach might be very useful if the goal is to use the mutant mice for drug development, we have illustrated the benefits of careful behavioral characterization in genetic models of basic brain processes as well. As mentioned above, it is unlikely that all aspects of a heterogeneous disease will be recapitulated in another species with a genetic mutation. Investigators must rely on convergence of behavioral and neuroanatomical or neurochemical data in a given mutant mouse to support clinical data on the link between the candidate gene and disease. No single phenotype such as PPI should be considered as being either necessary or sufficient to substantiate a model as having relevance to neuropsychiatric disease.

Animal studies addressing neuropsychiatric disease would benefit greatly from more neurobiologically based biomarkers for these disorders. 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 (Braff et al. 2007; Greenwood et al. 2007; Greenwood et al. 2011; Hokyo et al. 2010). Some of these genetic studies have generated further support for a genetic contribution to PPI (Greenwood et al. 2007, 2011), and other studies have suggested that genetic variants in COMT (Quednow et al. 2008; Roussos et al. 2008), CHRNA3

(Petrovsky et al. 2010), and neuregulin 1 (Roussos et al. 2011) directly affect PPI levels (as reviewed above). Thus, as human studies materialize with more neurobiologically defined behavioral measures, the ability to translate these measures or "endophenotypes" into animal models should improve dramatically. PPI in genetic models 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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Table 1

Genetically engineered model organisms based on genes related to: *vulnerability for schizophrenia*

References	Mouse strain, sex	Model description/background/ rationale	Basal PPI	Effects of drugs or manipulations typically used to induce PPI-deficits	Effects of (presumed) antipsychotics/other treatments
		DISC1			
Hikida et al. (2007)	DN-DISC1 TG, M	DISC1 is a potential SZ susceptibility gene	↓PPI in TG versus WT at lowest PP intensity only		
Ibi et al. (2010)	DN-DISC1 TG, combined with neonatal PolyI:C 5 mg/kg or saline (PND2-6), M & F	Two-hit model of SZ, genetic susceptibility combined with environmental insult (immune activation)	ØPPI & ØPA in TG versus WT		
Niwa et al. (2010)	DISC1 KD via *in utero* gene transfer (E14), M & F	DISC1 plays important role in brain development. In utero gene transfer allows for analysis of DISC1 function during development and impact on adult brain function	↓PPI & ØPA in KD versus WT at P56, ØPPI at P28, effect slightly less in F compared to M		*CLO*: ↑PPI & ØPA in KD; ØPPI & ØPA in WT
Lipina et al. (2010)	DISC1L100P point mutations	Missense mutation in exon 2 of DISC1 at L100P in mice	↓PPI & ↓PA in mutant versus WT	AMP (0.5 mg/kg) ↓PPI in mutant but ØPPI in WT	HAL: ↑PPI in mutant (↑PPI in WT at PP16); ↓PA in WT, ÆPA in mutant
Lipina et al. (2011)	DISC1L100P point mutation (combined with GSK3 mutant)	Missense mutation in exon 2 of DISC1 at L100P in mice; DISC1L100P mice crossed with Glycogen synthase kinase-3 (GSK-3), a serine/threonine protein kinase that interacts with the N-terminal region of DISC1	↓PPI in DISC1L100P mutant vs. WT; ØPPI in DISC1L100P × GSK-3α HET		TDZD-8 (GSK-3 inhibitor): ↑PPI & ØPA in DISC1L100P mutant; ØPPI & ØPA in WT
		Reelin			
Barr et al. (2008)	Reelin KO, M	Reelin levels in brains of SZ are reduced	Ø(unimodal acoustic) PPI, but ↓crossmodal PPI at 100 ms PP intervals, PPP at PP intervals ≤ 60 ms, ↓PA habituation & ↑PA at 100–110 dB(A) intensity for +/− versus WT		
		Neuregulin			
Chen et al. (2008)	Type III NRG1 mutants, M	NRG1 may represent a SZ susceptibility gene. Involved in	↓PPI & ØPA in +/− versus WT		Chronic NIC (↑PPI in +/−; ØPPI in WT)

References	Mouse strain, sex	Model description/background/ rationale	Basal PPI	Effects of drugs or manipulations typically used to induce PPI-deficits	Effects of (presumed) antipsychotics/other treatments
		cell-cell interaction; signals via erbB TK			
Duffy et al. (2008)	EGF-like domain NRG1 mutants, M	The EGF-like domain of NRG1 is sufficient for NRG's activity	ØPPI in −/− versus WT	MK801 (↓PPI in −/− versus WT); AMPH (↓PPI in −/− *and* WT; no significant differences between −/− & WT)	
Deakin et al. (2009)	NRG1$^{\text{Type 1-Tg}}$	Type I NRG1 increased in Hpc and PFC of SZ patients	↓PPI & ↑PA in Tg versus WT		
Barros et al. (2009)	ERBB2/B4-CNS-specific KO, M & F	NRG1 and ERBB4 are candidate genes for SZ	↓PPI in KO versus WT (M only; ØPPI in F); PA data not shown		CLO ↑PPI in KO; ØPPI in WT CLO ↑ spine density
Wen et al. (2010)	PV-Cre; ErbB4 KO	In adulthood NRG1 and ErbB4 may regulate neurotransmission. Evidence that ErbB4 is located at the postsynaptic density of excitatory neurons, likely on GABA interneurons	↓PPI & ØPA in −/− versus WT		*DIAZ*: ↑PPI in −/− mice; ØPPI in WT; PA data not shown
Kato et al. (2010)	NRG1 TG5, TG7, M & F	Postmortem studies indicate increased NRG1 in SZ brain. Transgenic mutants to examine hyper NRG1 signaling	ØPPI & ØPA in TG versus WT		
		COMT			
Papaleo et al. (2008)	COMT KO, COMT Val-Tg	Polymorphisms in COMT gene reported in SZ; mice overexpress human COMT-Val variant	ØPPI in −/− or TG versus WT; ↑PA in −/− versus WT, ↓PA in TG versus WT		
Tammimäki et al. (2010)	S-COMT KO, M & F	Two isoforms of COMT, S-COMT and MB-COMT, differentially contribute to DA function in the frontal cortex	ØPPI & ↑PA in −/− versus WT (although lack of ↑PA with ↑ dB in WT mice)		
		G-alpha			
Kelly et al. (2009)	Forebrain-specific Galpha OE, M, F	↑mRNA G-protein subunit Galpha levels, genetically linked to SZ	↓PPI & ØPA in +/− versus WT; developmental or adult expression ØPPI; ↓PPI correlates with ↓CTX & HPC cAMP levels		*HAL* ↑PPI in OE; ØPPI in WT *Rolipram* (↑*cAMP levels*): ↑PPI in OE; ØPPI in WT
		G72/G30			

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References	Mouse strain, sex	Model description/background/ rationale	Basal PPI	Effects of drugs or manipulations typically used to induce PPI-deficits	Effects of (presumed) antipsychotics/other treatments
Otte et al. (2009)	G72Tg (G72/G30 "humanized" BAC transgenic)	G72/G30 gene locus implicated in SZ, BD, and panic disorder	↓PPI & ØPA in Tg versus WT		HAL ↑PPI in Tg; ØPPI in WT (slight ↑PPI at low PP intensity in WT); PA data not reported
		SMARCA			
Koga et al. (2009)	SMARCA2 KO, M & F	SMARCA encodes BRM, a chromatin remodeling multi-protein complex; highly expressed in differentiating neurons; SNP in gene found in SZ (this paper)	↓PPI in −/− versus WT; PA data not shown		
		Neurexin			
Etherton et al. (2009)	Neurexin-1α KO, M & F	CNVs for neurexin-1 α identified in SZ & Autism. Neurexins bind to neuroligins and function as synaptic recognition molecules	↓PPI in −/− versus WT; ↑PA to stimuli 80–100 dB in −/− versus WT		
		TCF4			
Brzózka et al. (2010)	TCF4 Tg, M	TCF4, a helix-loop-helix transcription factor, identified in several GWAS studies as susceptibility gene for SZ	↓PPI & ØPA in Tg versus WT		
		AKT1			
Chen and Lai (2011)	AKT1 KO, M & F	AKT1 has been associated with schizophrenia in genetic studies as well as postmortem brain analyses. AKT1 signal transduction pathway important in diverse biological functions	*F*: ↓PPI & ØPA in −/− versus WT; PA *M*: ØPPI & ØPA in −/− versus WT		*RAC*: ØPPI & ØPA in −/− or WT (F only) *CLOZ*: ØPPI & ØPA in −/− or WT (F only) *8-OH-DPAT*: ØPPI in −/− versus WT (attenuation weak; no genotype × drug interaction) *SB216763*: ØPPI in −/− versus WT (attenuation weak; no genotype × drug interaction)

Abbreviations: *5-HT* serotonin, *AAV* adeno-associated virus, *A*β amyloid β- peptide, *ACE* angiotensin converting enzyme, *ACH* acetylcholine (receptor), *AD* Alzheimer's disease, *ADX* adrenalectomy, *AIL* advanced intercross line, *AMP* amphetamine, *AMY* amygdala, *APD* antipsychotic drug, *APP* amyloid precursor protein, *ARIP* aripiprazole, *APO* apomorphine, *AT* angiotensin, *BAC* bacterial artificial chromosome, *BACE* β-site APP cleaving enzyme, *BD* bipolar disorder, *BG* background, *CaMKIV* calcium-calmodulin-dependent protein kinase IV, *cAMP* cyclic adenosine monophosphate, *Ckr* chakragati, *CLO* clozapine, *CNS* central nervous system, *COC* cocaine, *COMT* catechol-O-methyltransferase, *CORT* corticosterone, *CRF* corticotropin releasing factor, *CTR* controls, *CTX* cortex, *DA* dopamine (receptor), *DAT* dopamine transporter, *dB* decibel, *DCC* deleted in colorectal cancer, *DIAZ* diazepam, *DIZ* dizocilpine, *DN* dominant-negative, *DDO* D-aspartate oxidase, *E* embryonic day, *EE* environmental enrichment, *EGF* epidermal growth factor, *ENU* N-ethyl-N-nitrosourea, *f* frontal, *F* female, *FABP* fatty acid binding protein, *FGF* fibroblast growth factor, *Fmr1* fragile × mental retardation 1 gene, *FMRP* fragile × mental retardation protein, *FXS* fragile × Syndrome, *GLAST* glutamate and aspartate transporter, *GLU* glutamate, *GluR* glutamate receptor, *GLUT* glucose transporter, *GR* glucocorticoid receptor, *GRIP* glutamate receptor interacting protein, *GSK* glycogen synthase kinase, *GWAS* genome wide association studies, *HAL* haloperidol, *HD* Huntington's disease, *HPC* hippocampus, *IC* imprinted cluster, *IL* interleukin, *ISI* interstimulus interval, *KI* knock-in, *KO* knock-out, *M* male, *m* metabotropic, *MDB* methyl-CpG binding protein, *mo* month, *NIC* nicotine, *MPEP* 2-methyl-6-(phenylethylyn)-pyridine hydrocholoride, *METH* metamphetamine, *Mgat* N-acetylglucosaminyltransferase, *NAA* N-acetyl-aspartate, *NAAG* N-acetylalpha L-aspartyl-L-glutamate, *NAC* nucleus accumbens, *NCAM* neural cell adhesion molecule, *NIS* nisoxetine, *nNOS* neuronal nitric oxide synthase, *NO* nitric oxide, *NPS* neuropeptide S (receptor), *NPY* neuropeptide Y, *NR* NMDA receptor

subunit, *NRG* neuregulin, *NRL* neuroligin, *ns* not significant(ly), *NSE* neuron-specific enolase, *NT* neurotensin, *OE* overexpressor, *OXO* oxotremorine, *PA* magnitude of response to pulse alone, *PACAP* pituitary adenylate-cyclase-activating polypeptide, *PD* Parkinson's disease, *PDE* phosphodiesterase, *PET-1* plasmocytoma expressed transcript-1, *PND* postnatal day, *PLC* phospholipase C, *PNS* prenatal stress, poly I:C polyinosinic: polycytidylic acid, *PP* prepulse, *PPI* prepulse inhibition of startle, *PPP* prepulse potentiation, *PS1* presinilin1, *PWS* Prader–Willi syndrome, *QTL* quantitative trait locus, *QUET* quetiapine, *RAC* raclopride, *RAGE* receptor for advanced glycation end-products, *RasGAP* Ras GTPase-activating protein, *RE* renin-enhancer, *RIS* risperidone, *SCOP* scopolamine, *SI* social isolation, *SNP* single nucleotide polymorphism, *SOCS* suppressor of cytokine signaling; *SREB* superconserved receptor expressed in brain; *STR* striatum, *SYN* synapsin, *SynGAP* synaptic GTP-ase-activating protein, *SZ* schizophrenia, *TAAR* trace amine-associated receptor, *TG* transgenic, TGF-β transforming growth factor beta, *TK* typosine kinase, *TMS* transcranial magnetic stimulation, *V1b* vasopressin receptor 1b, *WT* wild-type

↓ decreased, ↑ increased, Ø unchanged, −/− homozygous mice, +/− heterozygous mice

Table 2

Genetically engineered model organisms based on genes related to: *neurotransmitters, neuropeptides, and orphan receptors*

References	Mouse Strain, Sex	Model description/background/ rationale	Basal PPI	Effects of drugs or manipulations typically used to induce PPI-deficits	Effects of (presumed) antipsychotics/ other treatments
			A. DOPAMINE		
		DA receptors			
Doherty et al. (2008)	DA D1, D2 & D3 KO, M, F	Abnormalities in DA signaling in SZ patients in part have led to the DA hypothesis for SZ	ØPPI in D1, D2 & D3 −/− versus WT; ↑PA in D1 −/− versus WT; ØPA in D2 (M only); ↓PA in D2 −/− (F only) & D3 −/− versus WT & in D3 (F) versus D3 (M) −/−	COC (ØPPI in D1 −/−; ↓PPI in D2 −/−, D3 −/− & WT mice; but: attenuated ↓PPI in D2−/− versus WT and more pronounced ↓PPI in D3 −/− versus WT; ØPA in WT	RAC; SCH23390 (a D1 antagonist) both ↓COC-induced PPI deficits in WT; ØPA in WT)
Young et al. (2011b)	DA D4 KO, M	Alterations in D4R may contribute to cognitive and attentional deficits in neuropsychiatric disorders.	ØPPI & ØPA in −/− or +/− versus WT		
		DAT			
Powell et al. (2008)	DAT KO, (F) M	A hyper-DA state and DAT abnormalities have been implicated in SZ	M: ↓PPI & ØPA in −/− versus WT; F: inconsistent ↓PPI in −/− versus WT		M: CLO (PPI in −/− normalized to WT levels, but ØPPI in −/− & WT versus VEH) ↓PA (main effect); QUET (↑PPI & ØPA in −/− & ØPPI & ↓PA in WT)
		Other Dopamine related			
Grant et al. (2007)	DCC KO, M (PPI studies)	DCC mice are netrin 1 receptor KO mice. Netrin 1 is strongly expressed on and may affect development of DA neurons	↓PPI (yet ns) and ↑PA (trend only) in +/− versus +/+	ØAMP (ØPPI in +/−, but ↓PPI in +/+)	
			B. GLUTAMATE		
		NR1			
Duncan et al. (2010)	NR1 hypomorph (NR1 $^{neo/neo}$),	Developmental effects of NR1 hypomorph on other Glu receptors could contribute to the SZ-like phenotype. Evidence for alterations in kainic acid receptors in SZ.	↓PPI & ↑PA in hypomorph versus WT		LY382884, kainic acid antagonist, ↓PA in hypomorphs & ØPA in WT; ↑PPI in hypomorphs & WT
Belforte et al. (2010)	Early postnatal NR1 reduction in GABA interneurons *(Ppp1r2-cre* +/−*;*	NMDAR hypofunction, specifically in GABA interneurons, may contribute to SZ pathophysiology. NR1 is an obligatory subunit of NMDAR.	Early postnatal NR1 reduction: ↓PPI & ØPA in KO versus Ctrl lines (Flox-A & Cre), in isolated & group-housed mice		

References	Mouse Strain, Sex	Model description/background/ rationale	Basal PPI	Effects of drugs or manipulations typically used to induce PPI-deficits	Effects of (presumed) antipsychotics/ other treatments
	*NR1*loxP/loxP-line A [KO]), M		Adult NR1 reduction: ØPPI & ØPA		
		AMPA			
Sagata et al. (2010)	GluR4 KO, M & F	GluR4 subunit of AMPA receptor involved in synaptic plasticity; genetic association between GluR4 and SZ	↓PPI & ↓PA in −/− versus WT		
		mGLU			
Gray et al. (2009)	mGlu5 KO, M, F	mGlu5 receptor interacts with NMDA receptor and has been implicated in behavioral endophenotypes of SZ	↓PPI in −/− versus WT; ØPA in −/− versus WT		Chronic (8 wks) CLO (↑PPI in −/− & ØPPI in WT); ↑NMDA receptors with CLO treatment
Fendt et al. (2010)	mGlu8 KO, M	mGlu8 is a presynaptic receptor which regulates Glu release; may be important for neuropsychiatric disorders with altered Glu function (e.g. SZ).	ØPPI and ↓PA in −/− versus WT	PCP: ↓PPI in −/− and WT; ØPA in −/− or WT	
Chen et al. (2010)	mGlu5 KO, M & F	Evidence of NMDA hypofunction in mGlu5 KO mice; mGlu5 KO mice may be useful as novel screen of putative glutamatergic antipsychotics.	↓PPI & ØPA in −/− versus WT		Sarcosine: ↑PPI in −/−; ØPPI in WT; ØPA in −/− or WT LY379268: ØPPI & ØPA in −/− or WT N-acetylcysteine: ↑PPI in −/− & WT; ↑PPI in −/− not blocked with LY341495
		Vesicular glutamate transporter			
Wallén-Mackenzie et al. (2009)	VGLUT2$^{f/f;CKII/Cre}$ (preadolescent forebrain-specific KO), M & F	Forebrain glutamate plays an important role in many sensory and cognitive functions relevant to psychiatric disease; downstream changes in DA (this study)	↓PPI & ↓PA in VGLUT2$^{f/f;CKII/Cre}$ versus WT	PCP: ↓PPI in WT; ØPPI in VGLUT2$^{f/f;CKII/Cre}$ (no drug versus post-PCP); PA (no data shown)	ARIP (no-drug versus post-ARIP): ↑PPI in KO; ØPPI in WT; PA (no data shown)
		Glycine			
Benneyworth et al. (2011)	SR KO, M GCP2 HET, M	D-serine is an agonist and NAG an antagonist at the glycine modulatory site on NMDA receptors. Serine racemate (SR) and glutamic acid decarboxylase 2 (GCP2) regulate D-serine and NAG, respectively.	ØPPI & ØPA in SR −/− versus WT; ØPPI & ØPA in GCP2 +/− versus WT	PCP: ↓PPI in SR −/−, GCP2 +/−, & WT; inverted U-shaped dose response function on PA: high dose (6 mg/kg) ØPA in WT, ↑PA in SR −/−; 3 mg/kg dose ↑PA in WT, ØPA in GCP2 +/− AMPH: ↓PPI in Sr−/−, GCP2 +/−, & WT; U-shaped dose response function on PA; no difference in SR −/−, GCP2 +/−,	

References	Mouse Strain, Sex	Model description/background/ rationale	Basal PPI	Effects of drugs or manipulations typically used to induce PPI-deficits	Effects of (presumed) antipsychotics/ other treatments
				& WT	
		Other glutamate related			
Karlsson et al. (2009)	GLAST (EAAT1) KO, M, F	Glutamate dysfunction associated with SZ; glutamate transporter may be useful pharmacological target for SZ.	ØPPI in −/− or +/− versus WT; ↓PA in −/− versus +/− & WT		
Guo et al. (2009)	SynGAP +/− gene deletion	SynGAP is a RasGAP and NMDAR-associated protein; interacts with NMDA receptors	↓PPI and ↑PA in +/− versus WT		CLO: ØPPI in +/− or WT; ↓PA in +/− and WT
Han et al. (2009)	GCPII +/−, M & F	Glutamate carboxypeptidase II (GCPII) hydrolyzes NAAG into glutamate and NAA	ØPPI & ØPA in +/− versus WT		
Wang et al. (2009)	Norbin KO	Norbin interacts with mGluR5 receptors and positively regulates mGluR5 signaling.	↓PPI & ØPA in −/− versus WT		
		C. SEROTONIN (5-HT)			
Semenova et al. (2008)	5-HT7 KO, M	Antipsychotics have high affinity for 5-HT7 receptors.	ØPPI across PP intensities and ISI, ØPA	PCP ↓PPI in WT, attenuated in −/−; Apo and Amp ↓PPI in WT & −/−; ØPA with Apo, Amp, PCP	
Shanahan et al. (2009)	5-HTT KO, F	OCD patients have PPI deficits; gain of function 5-HTT alleles associated with OCD	ØPPI in −/−, +/− versus WT	RU24969 (5HT1B agonist) ↓PPI in WT, ØPPI in −/−, intermediate effect in +/−	
Schaefer et al. (2009)	Pet-1 KO, M &F	Pet-1 is a transcription factor restricted to 5-HT neurons. Gene deletion results in loss of 5-HT.	↑PA & ØPPI in −/− versus WT		
Hill et al. (2011)	5HT2C KO	5HT and BDNF interact; ↑BDNF levels 5HT2C KO mice (this study)	ØPPI & ØPA in −/− versus WT		
Groenink et al. (2011)	5HT1A KO, M (129S6, Swiss Webster [SW] backgrounds)	5HT1A gene may interact with adverse life events.	ØPPI & ØPA in −/− versus WT	129S6: Maternal separation ↓PPI & ↑PA in −/− & WT SW: Maternal separation ØPPI & ØPA in −/− & WT	
van den Buuse et al. (2011a)	5HT1A KO, M & F	5HT1A receptor may mediate effects of MDMA on PPI	ØPPI & ØPA in −/− versus WT	MDMA: ↓PPI in −/− at lower doses than WT at 100 ms ISI (M only); ↓PA in −/− & WT	
van den Buuse et al. (2011b)	5HT1A KO, M & F	5HT1A receptor may interact with neurotransmitter systems involved in SZ	ØPPI & ØPA in −/− versus WT	APO: ↓PPI & ØPA in −/− & WT	
		D. ACETHYLCHOLINE (ACh)			
		Nicotinic			

References	Mouse Strain, Sex	Model description/background/ rationale	Basal PPI	Effects of drugs or manipulations typically used to induce PPI-deficits	Effects of (presumed) antipsychotics/ other treatments
Darvas et al. (2009)	LYPD6 Tg	LYPD6 modulates nicotinic ACh receptors; LYPD6 Tg show enhanced nicotinic tone	↑PPI in Tg versus WT; ØPA in Tg versus WT		
Young et al. (2011a)	α7-nAChR KO, M & F	α7-nAChR is being investigated as a pro-cognitive target for SZ; comparison of KO mice across several cognitive tests	ØPPI in −/−, +/−, and WT; ↑PA in −/− versus +/− & WT;		
		Muscarinic			
Turner et al. (2010)	M2, M4 KO, M	M2 and M4 muscarinic acetylcholine receptors differ in tissue distribution and physiology; may play a role in sleep and arousal	ØPPI in M2 or M4 −/− versus C57BL/6 N mice; ØPA in M2 −/− versus M4 −/−; ↑PA in M2 −/− versus C57; ØPA in M4 −/− versus C57 (store bought mice; not littermates)		
Thomsen et al. (2010)	M1, M4 KO, F M1KO/ M4KO,M,F	Muscarinic receptors may be related to pathophysiology of SZ, and muscarinic agonists have been proposed as targets for antipsychotics and cognition enhancers	F: ↓PPI & ØPA in M1−/−/ M4−/− versus WT; ØPPI & ØPA in M1 −/− versus WT; ØPPI & ↑PA in M4 −/−WT; M: ØPPI & ØPA in M1−/−/M4−/− versus WT	SCOP: ↓PPI in WT & M4−/− mice (F) & slight ↓PPI in M1−/−/ M4−/− (M); ØPPI in M1−/− (F) or M1−/−/M4−/− (F) ↑PA in all groups; M1−/−/ M4−/− (F) and M4−/− (F) more sensitive to ↑PA	Xanomeline: blocked SCOP-induce ↓PPI in WT & M1−/−, but not in M4−/− mice; data in M1−/−/ M4−/− difficult to interpret because ØPPI with SCOP; blocked SCOP-induced ↑PA in M1−/− & M1−/−/M4−/−; ØPA in SCOP-treated M4−/− OXO (versus SCOP): blocked SCOP-induced ↓PPI in all genotypes (although SCOP effect not significant in M1−/−/M4−/−); trend for reversal of SCOP-induced ↑PA OXO (alone): ↓PPI in WT & ↑PPI in M1−/−/ M4−/−; ↓PA in WT & M1−/−M4−/− (which may lead to variability in PPI) CLO: ↑PPI in M1−/−/M4−/− at doses with ØPPI in WT; ↓PPI in WT & M1−/−; ØPPI in M4−/−; ↓PA in WT & M1−/−; ØPA in M1−/−/ M4−/− & M4−/− HAL: ↑PPI in WT & M1−/−/M4−/−; ØPA in WT or M1−/−/M4−/−
		Vesicular ACh Transporter (VAChT)			

References	Mouse Strain, Sex	Model description/background/ rationale	Basal PPI	Effects of drugs or manipulations typically used to induce PPI-deficits	Effects of (presumed) antipsychotics/ other treatments
Schmid et al. (2011)	VAChT KD, M	Cholinergic transmission associated with cognitive function and startle behavior. VAChT KD mice have reduced cholinergic tone.	ØPPI & ØPA in −/− versus WT; ↓ between day HAB in −/− versus WT		
		E. (NEURO)PEPTIDES			
		Angiotensin/Renin			
Martin et al. (2008)	RE KO, NSE-AT1 TG, M	AT/Renin may be involved in brain (DA) signaling. ACE levels were reported to be altered in SZ patients. REKO have reduced renin signaling; NSE-AT1 TG have over-expression of AT1 receptors.	ØPPI (RE −/− & NSE-AT1 TG vs. WT); ↓PA (RE KO (trend)) & ØPA in NSE-AT1 versus WT	APO, AMP & DIZ (all ↓PA (RE KO vs. WT; main effect across treatment conditions); ↓PPI in RE −/−, NSE-AT1 TG & WT (no genotype × drug interactions); APO (↓PA in RE −/−, NSE-AT1 TG & WT); AMP (↑PA in RE −/− & WT (trend), ØPA in NSE-AT1 TG & WT;) DIZ (↑PA in RE −/− & WT; more pronounced in RE −/−, ↑PA (trend) in NSE-AT1 TG & WT;	
		Neurotensin			
Feifel et al. (2010a)	NT1 KO, M & F	Neurotensin (NT) may play a role in SZ pathophysiology. NT levels decreased in CSF from SZ patients, and APDs increase NT levels.	ØPPI in −/− versus WT; ØPA in −/− versus WT	AMP ↓PPI & ØPA in −/− & WT; MK801 ↓PPI; MK801 ↑PA (low dose only; more pronounced in WT than −/−)	PD149163, NT1 receptor agonist, ↑PPI in WT, ØPPI in −/−;
Feifel et al. (2010b)	NT2 KO, M & F	NT2 receptors highly expressed in brain but not well studied	↑PPI & ↓PA in −/− versus WT (both sexes)		
Oliveros et al. (2010)	NT1 KO & NT2 KO, M	NT receptors may play a role in psychotomimetic and antipsychotic effects of drugs	ØPPI & ØPA in NT1 −/−, NT2 −/−, & WT	AMP: ↓PPI in NT2 −/− & WT, ØPPI in NT1 −/−; ↓PA in WT, ØPA in NT1 −/− or NT2 −/− DIZ: ↓PPI in NT2 −/− & WT, ØPPI in NT1 −/−	CLO: blocks AMP-induced ↓PPI in WT & NT2 −/− ; blocks DIZ-induced ↓PPI in WT, does not block DIZ-induced ↓PPI in NT2 −/− NT69L: blocks AMP-induced ↓PPI in WT & NT2 −/−; blocks DIZ-induced ↓PPI in NT2 −/−, does not block DIZ-induced ↓PPI in WT; ↓PA in WT & NT2−/−
		CRF			
Groenink et al. (2008)	CRF-OE, M	Stress physiology, particularly CRF and glucocorticoids, implicated in neuropsychiatric disorders	↓PPI in CRF-OE versus WT at lower PP intensities; ØPA in CRF-OE versus WT	CORT implant: ØPPI in CRF-OE or WT mice.	CRF1 antagonists CP154,526 & DMP695 normalized PPI deficit in CRF-OE mice; GR

References	Mouse Strain, Sex	Model description/background/ rationale	Basal PPI	Effects of drugs or manipulations typically used to induce PPI-deficits	Effects of (presumed) antipsychotics/ other treatments
					antagonists and ADX did not; CP154,526 ↓PA
		Oxytocin			
Caldwell et al. (2009)	Oxt KO, M, F	Oxytocin has shown antipsychotic potential in animal models of SZ and in some preliminary clinical trials	ØPPI & ØPA in −/− versus WT	PCP: Exacerbated ↓PPI in −/− versus WT, ØPA; Apo & Amp: ↓PPI in −/− & WT; ØPA	
		Arginine Vasopressin			
Egashira et al. (2009)	V1aR KO, V1bR KO	Arginine vasopressin (AVP), a diuretic peptide with receptors widely expressed in the CNS, has been implicated in neuropsychiatric disorders.	↓PPI in V1aR & V1bR −/− versus WT; ↑PA in V1aR & V1bR −/− versus WT		
		Neuropeptide Y			
Karl et al. (2010a)	Y2 KO, M & F	NPY levels altered in SZ patients. NPY Y2 receptor expressed in HPC and AMY	M: ↑PPI & ØPA in −/− versus WT F: ØPPI in −/− versus WT	MK801: ↓PPI & ↑PA in −/− & WT AMP: ↓PPI & ↑PA in −/− & WT	
Karl et al. (2010b)	Y1 KO, M	Decreased Y1 receptor expression in lymphocytes of SZ patients	ØPPI, ↓PA, & ↓HAB in −/− versus WT	MK801: ↓PPI & ↑PA in −/− & WT AMP: ↓PPI & ØPA in −/− & WT (effects are ISI & PP dependent)	
		Neuropeptide S			
Zhu et al. (2010)	NPSR1 KO, M & F	NPSR1 is a G protein coupled receptor located in brain regions involved in anxiety and learning and memory, whose endogenous ligand is NPS. NPSR1 SNPs identified in panic disorder.	M: ↓PA & ØPPI in −/− versus WT; F: ØPA & ØPPI in −/− versus WT		
Fendt et al. (2011)	NPSR KO, M	NPS implicated in regulation of emotional behavior	ØPPI in −/− or +/− versus WT; ↓PA in −/− & +/− versus WT		HAL: ↑PPI & ↓PA in −/−, +/−, & WT
		PACAP			
Hashimoto et al. (2007)	PACAP KO, M	PACAP affects neurotransmission; potential SZ susceptibility gene	↓PPI in −/− versus WT		RIS (↑PPI in −/−; Ø in WT)
Ishihama et al. (2010)	PACAP KO, M	Genetic susceptibility plus environmental factors may contribute to SZ	↓PPI in −/− versus WT (PA data not shown)	SI: ↓PPI & ØPA in −/− & WT	EE: ↓PPI in −/− & WT
		Relaxin-3			

References	Mouse Strain, Sex	Model description/background/ rationale	Basal PPI	Effects of drugs or manipulations typically used to induce PPI-deficits	Effects of (presumed) antipsychotics/ other treatments
Smith et al. (2009)	Relaxin-3 KO, M & F	Relaxin-3 modulates feeding, stress response, exploratory behavior, and arousal	ØPPI in −/− versus WT; PA data not reported		
		F. ORPHAN RECEPTORS			
Matsumoto et al. (2008)	SREB2 KO, SREB2 TG, M	SREB (= GPR85) highly conserved GPCR; expressed in brain regions of high plasticity; overtransmission of 2 SNPs in SZ (this study)	↓PPI & ØPA in TG versus WT; ØPPI & ØPA in −/− versus WT		
Logue et al. (2009)	GPR88 KO, M & F	GPR88 is highly expressed in brain regions implicated in SZ and regulates DA function (this paper).	↓PPI in −/− versus WT; ØPA in −/− versus WT		HAL: ↑PPI in −/−, ØPPI in WT; ↓PA in −/− & WT RISP: ↑PPI in −/− & WT; ↓PA in −/− & WT
Kim et al. (2010)	TAK1 KO, M	TAK1 is a nuclear orphan receptor that regulates transcription; TAK1 deletion delays migration of cerebellar granular neurons	↓PPI, ↓PA, ↓HAP in −/− versus WT		
		G. TRACE AMINES			
Karmacharya et al. (2011)	TAAR1 KO, M	Trace amines are very similar to biogenic amines and are implicated in neuropsychiatric disease; trace amine receptors may mediate effects of antipsychotic drugs	ØPPI in −/− versus WT (PA data not shown)		CLO: ↑PPI in WT, ØPPI in −/−

Abbreviations: *5-HT* serotonin, *AAV* adeno-associated virus, *Aβ* amyloid β- peptide, *ACE* angiotensin converting enzyme, *ACH* acetylcholine (receptor), *AD* Alzheimer's disease, *ADX* adrenalectomy, *AIL* advanced intercross line, *AMP* amphetamine, *AMY* amygdala, *APD* antipsychotic drug, *APP* amyloid precursor protein, *ARIP* aripiprazole, *APO* apomorphine, *AT* angiotensin, *BAC* bacterial artificial chromosome, *BACE* β-site APP cleaving enzyme, *BD* bipolar disorder, *BG* background, *CaMKIV* calcium-calmodulin-dependent protein kinase IV, *cAMP* cyclic adenosine monophosphate, *Ckr* chakragati, *CLO* clozapine, *CNS* central nervous system, *COC* cocaine, *COMT* catechol-O-methyltransferase, *CORT* corticosterone, *CRF* corticotropin releasing factor, *CTR* controls, *CTX* cortex, *DA* dopamine (receptor), *DAT* dopamine transporter, *dB* decibel, *DCC* deleted in colorectal cancer, *DIAZ* diazepam, *DIZ* dizocilpine, *DN* dominant-negative, *DDO* D-aspartate oxidase, *E* embryonic day, *EE* environmental enrichment, *EGF* epidermal growth factor, *ENU* N-ethyl-N-nitrosourea, *f* frontal, *F* female, *FABP* fatty acid binding protein, *FGF* fibroblast growth factor, *Fmr1* fragile × mental retardation 1 gene, *FMRP* fragile × mental retardation protein, *FXS* fragile × Syndrome, *GLAST* glutamate and aspartate transporter, *GLU* glutamate, *GluR* glutamate receptor, *GLUT* glucose transporter, *GR* glucocorticoid receptor, *GRIP* glutamate receptor interacting protein, *GSK* glycogen synthase kinase, *GWAS* genome wide association studies, *HAL* haloperidol, *HD* Huntington's disease, *HPC* hippocampus, *IC* imprinted cluster, *IL* interleukin, *ISI* interstimulus interval, *KI* knock-in, *KO* knock-out, *M* male, *m* metabotropic, *MDB* methyl-CpG binding protein, *mo* month, *NIC* nicotine, *MPEP* 2-methyl-6-(phenylethylyn)-pyridine hydrocholoride, *METH* metamphetamine, *Mgat* N-acetylglucosaminyltransferase, *NAA* N-acetyl-aspartate, *NAAG* N-acetylalpha L-aspartyl-L-glutamate, *NAC* nucleus accumbens, *NCAM* neural cell adhesion molecule, *NIS* nisoxetine, *nNOS* neuronal nitric oxide synthase, *NO* nitric oxide, *NPS* neuropeptide S (receptor), *NPY* neuropeptide Y, *NR* NMDA receptor subunit, *NRG* neuregulin, *NRL* neuroligin, *ns* not significant(ly), *NSE* neuron-specific enolase, *NT* neurotensin, *OE* overexpressor, *OXO* oxotremorine, *PA* magnitude of response to pulse alone, *PACAP* pituitary adenylate-cyclase-activating polypeptide, *PD* Parkinson's disease, *PDE* phosphodiesterase, *PET-1* plasmocytoma expressed transcript-1, *PND* postnatal day, *PLC* phospholipase C, *PNS* prenatal stress, poly I:C polyinosinic: polycytidylic acid, *PP* prepulse, *PPI* prepulse inhibition of startle, *PPP* prepulse potentiation, *PS1* presinilin1, *PWS* Prader–Willi syndrome, *QTL* quantitative trait locus, *QUET* quetiapine, *RAC* raclopride, *RAGE* receptor for advanced glycation end-products, *RasGAP* Ras GTPase-activating protein, *RE* renin-enhancer, *RIS* risperidone, *SCOP* scopolamine, *SI* social isolation, *SNP* single nucleotide polymorphism, *SOCS* suppressor of cytokine signaling; *SREB* superconserved receptor expressed in brain; *STR* striatum, *SYN* synapsin, *SynGAP* synaptic GTP-ase-activating protein, *SZ* schizophrenia, *TAAR* trace amine-associated receptor, *TG* transgenic, TGF-β transforming growth factor beta, *TK* typosine kinase, *TMS* transcranial magnetic stimulation, *V1b* vasopressin receptor 1b, *WT* wild-type

↓ decreased, ↑ increased, Ø unchanged, −/− homozygous mice, +/− heterozygous mice

Table 3

Genetically engineered model organisms based on genes related to: *miscellaneous biological processes*

References	Mouse strain, sex	Model description/background/rationale	Basal PPI	Effects of drugs or manipulations typically used to induce PPI-deficits	Effects of (presumed) antipsychotics/other treatments
		Second messengers			
Siuciak et al.(2008)	PDE4B KO, M	PDE4 catalyzes the degradation of cAMP. Widely expressed in brain	↓PPI & ↑PA in −/− versus WT (↓PPI not dependent on ↑PA)		
McOmish et al.(2008)	PLC-β1 KO	PLC-β1 is a rate-limiting enzyme involved in the intracellular signaling cascade linked to several metabotropic receptors implicated in SZ; PLC-β1 reduced in SZ brain	↓PPI & PA (−/− vs. WT)		*EE (main effects)*: ↑PPI & ↓PA (trend) versus standard housing); EE × genotype × PP intensity effect on PPI (↑PPI in −/−); EE × genotoype effect on PA (↓PA in WT); HAL (no rescue of PPI deficit of −/− vs. VEH treated WT; ØPA); CLO (main effect ↑PPI; genotype × CLO × PP intensity effect: rescue of PPI deficit of −/− vs. VEH treated WT; main effect: ↓PA vs. VEH; genotype × CLO; more pronounced ↓PA in WT)
Koh et al.(2008)	PLC-β1 KO		↓PPI & trend for ↓PA (−/− vs. WT)		*HAL* normalized PPI in −/−, no effect in WT; ØPA
		Growth factors			
Ransome et al.(2008)	SOCS-2 TG	SOCS-2 affects growth hormone signaling & potentially hippocampal neurogenesis	ØPPI in TG versus WT		
Scearce-Levie et al.(2008)	Fgf17 KO, M & F	Fgf17 is involved in region-specific development of the rodent fCTX	ØPPI & ØPA in −/− versus +/− or WT		
Ohgake et al.(2009)	Mdk KO, M & F	Midkine involved in neurodevelopment and adult neuroplasticity; abnormal serum levels in SZ and AD; KO produces ↓DA and DAR in striatum (this paper)	↓PPI in −/− versus WT, +/− intermediate (adult); ØPPI in −/− versus WT (4 wk old); ØPA in −/−, +/−, WT (adult, 4wk)		*HAL* ↑PPI in −/−; ØPPI in WT *CLO* ↑PPI in −/−; ØPPI in WT Overall ↓PA with APD; CLO (3 mg/kg) ↓PA in WT

References	Mouse strain, sex	Model description/background/rationale	Basal PPI	Effects of drugs or manipulations typically used to induce PPI-deficits	Effects of (presumed) antipsychotics/other treatments
Sun et al.(2010)	Forebrain-specific SMAD4 KO, M	SMAD4 is an intracellular transducer of TGF-β signaling; TGF-β signaling important for neurodevelopment and shown to be abnormal in SZ	↓PPI & ØPA in −/− versus WT		
Nguyen et al.(2011)	PDGFR-β $^{f/f;Nestin\ Cre+}$ KO, M (neuron-specific PDGFR KO)	Platelet derived growth factor (PDGF) is important for embryogenesis and CNS development. PDFGR-β has been associated with SZ and ASD	↓PPI & ØPA in −/− versus WT		
		Protein kinase			
Bersudsky et al.(2008)	GSK3β KO, M	GSK3β levels were reported to be reduced in SZ patients. Li inhibits GSK3β *in vitro*	ØPPI & ØPA in +/− versus WT		
Kaidanovich-Beilin et al.(2009)	GSK3α KO, M & F	GSK3 implicated in several neuronal signaling pathways	↑PPI & ØPA in −/− versus WT		
Takao et al.(2010)	CaMKIV KO, M	CaMKIV is a protein kinase that activates transcription factor CREB and thus may play a role in synaptic plasticity	ØPPI & ØPA in −/− versus WT		
Siuta et al.(2010)	Rictor $^{f/f;Nestin\ Cre+}$ KO (neuron-specific Rictor KO)	Rictor is a component of mTOR2C, the kinase responsible for phosphorylation of Akt. Akt deficiencies associated with SZ	↓PPI & ØPA in −/− versus WT		*NIS* (↑PPI in −/−; no data in WT; PA data not shown) *CLO* (ØPPI in −/−; PA data not shown)
		Proteases			
Horii et al.(2008)	Neuropsin KO, M	The serine protease neuropsin may be involved in neuronal plasticity/ degeneration	ØPPI & PA in −/− versus WT		
Savonenko et al.(2008)	BACE1 KO, M	BACE1 is critical for APP cleavage/ amyloid β production. May also play a role in SZ via proteolysis of NRG & axon myelination	↓PPI in −/− & ØPPI in +/− versus WT; ØPA in −/− & +/− versus WT; ↑PA latency in −/− versus +/− & WT		*CLO:* (amelioration of PPI deficits in −/−; ØPPI in +/− & WT)
		Synaptic proteins			
Dyck et al.(2007)	SYN II KO	SYN II, a vesicle-linked phosphoprotein plays a role in neuronal development & transmitter release; hypothesized to contribute to the etiology of SZ	↓PPI (−/− relative to +/− & WT)		
Dyck et al.(2009)	SYN II KO, M & F	↓SYNII in mPFC of SZ patients; ↑SYNII levels with chronic APD	↓PPI in −/− versus +/− and WT; ↓PA in −/− versus +/− and WT; lack of HAB in −/−		

References	Mouse strain, sex	Model description/background/rationale	Basal PPI	Effects of drugs or manipulations typically used to induce PPI-deficits	Effects of (presumed) antipsychotics/other treatments
Savonenko et al.(2009)	EP2 KO, F	EP2 is a prostaglandin receptor involved in activity-dependent synaptic plasticity	↓PPI in −/− versus WT; ØPA in −/− versus WT		
Oliver and Davies (2009)	SNAP-25 *Bdr* (*Blind drunk* mutant), SNAP-25 +/−, combined with prenatal stress (PNS), M	SNARE protein SNAP-25 important for synaptic function and neurotransmitter release; SNAP-25 genomic region linked to SZ	↓PPI & ØPA in *Bdr* mutant versus WT, ↓PPI exacerbated by PNS; ØPPI & ØPA in +/− versus WT, no effect of PNS in +/−		*CLO* ↑PPI in BDR/NS & BDR/PNS; ØPPI in WT/NS or WT/PNS *HAL* ↑PPI in Bdr/PNS at 86dB PP only; ØPPI in WT/NS, Bdr/NS, or WT/PNS
Blundell et al.(2010)	Rim1α KO, M Rab3A KO, M Syt1R233Q (point mutation) KI, M&F Rim1αS413A KI, M	Presynaptic proteins involved in neurotransmitter release and associated with SZ in genetic studies	*Rim1α*: ↓PPI &ØPA in −/− versus WT *Rab3A* ↓PPI & ØPA in −/−versus WT *Syt1R233Q* ↓PPI & ØPA in KI versus WT *Rim1α S413A* ØPPI & ØPA in KI versus WT		
		Calcium Signaling			
Matsuo et al.(2009)	RyR3 KO	Ryanodine receptor 3 is an intracellular calcium release channel preferentially expressed in HPC and STR and involved in synaptic transmission and plasticity. RyR3 forms a signaling complex with calcineurin, a potential susceptibility gene for SZ and BD	↓PPI in −/− versus WT at 78 dB PP + 110 dB startle pulse only; ØPA in −/− versus WT		
Nakagawasai et al.(2010)	$Ca_v2.2$ KO, M	N-type calcium channels are important for neurotransmitter release, brain development, and activity-depdendent plasticity	↓PPI & ØPA in −/− versus WT		
		Potassium channel signaling			
Kapfhamer et al.(2010)	Ppp2r5δ KD, M & F GSK3β KD, M KCNQ2 KD, M & F KD created via gene trap (GT), reduced expression by 50%	KCNQ2 gene encodes an M-type potassium channel subunit and may be a substrate for GSK3β; PP2A regulates GSK3β; GSK3β and M-type potassium channels may be linked to SZ	*Ppp2r5δGt*: ↓PPI & ØPA in GT/+ versus WT *GSK3β*: ↓PPI & ØPA in +/− versus WT *KCNQ2* ↓PPI & ØPA in +/− versus WT		
		Immune activation			
Smith et al.(2007)	IL6 KO	Maternal immune activation (here simulated via poly I:C injection) has		*Maternal poly I*:C injection.	

References	Mouse strain, sex	Model description/background/rationale	Basal PPI	Effects of drugs or manipulations typically used to induce PPI-deficits	Effects of (presumed) antipsychotics/other treatments
		been implied in the pathogenesis of SZ		*Effects in offspring*: ØPPI in −/− but ↓PPI in WT	
Asp et al.(2010)	Tap1 KO mice	Prenatal influenza infection associated with increased SZ risk. Transporter associated with antigen processing 1 mice have reduced expression of MHC class I	No direct comparisons between −/− and WT mice. C57BL6/J WT mice purchased from Jackson Laboratories	Influenza infection on PND 3 or 4: ↓PPI in adult −/− mice (during ISI block), trend for ↑PA in infected mice in startle threshold block; ØPPI & ØPA in infected versus non-infected WT C57 mice	
López-Ramos et al.(2010)	TgIE96, M	Mice expressing pseudorabies virus immediate-early protein IE180 (TgIE96) have cerebellar abnormalities	↓PPI & ØPA in Tg versus WT (C57BL/6J WT mice purchased from Jackson Laboratories)		
		Glucose metabolism			
Schmidt et al.(2008)	GLUT3 (Slc2a3) KO, M	GLUT is widely expressed in brain. Role in neuronal glucose homeostasis and likely role in diverse behaviors	↓PPI at lower PP intensities & ↑PA in +/− versus WT		
		Neuromodulatory functions			
Errico et al.(2008)	DDO KO, M	The enzyme DDO degrades D-aspartate, an amino acid with elusive function in the CNS. A neuromodulatory function at NMDA receptors has been implied	ØPPI & ØPA in −/− versus WT	AMP (ØPPI in DDO −/−; ↓PPI in WT) DIZ (↓PPI in −/− & WT, more pronounced in WT)	Chronic D-aspartate (ØPPI & PA) antagonized AMP & DIZ-induced ↓PPI in WT (not tested in −/−)
Tanda et al.(2009)	nNOS KO, M	nNOS synthesizes NO from L-arginine; involved in many intracellular signaling processes; ↓nNOS expression in STR and HPC of SZ; polymorphisms of nNOS associated with SZ	ØPPI & ØPA in −/− versus WT	*SKF81297 (DA D1 agonist)* ↓PPI & ØPA in −/−; ØPPI & ↓PA in WT	
		Altered myelination			
Tanaka et al.(2009)	$PLP1^{(tg/-)}$	Mylein and oligodendrocyte dysfunction may contribute to schizophrenia pathogenesis. Myelin proteolipid protein (plp1) decreased in brains of SZ patients	↓PPI in Tg versus WT at higher PP intensity (78dB), PA data not shown		
		Spine morphogenesis			
Cahill et al.(2009)	KALRN KO	Kalrinin, a guanine-nucleotide exchange factor (GEF) for Rac-like GTPases, regulates spine morphogenesis.	↓PPI in −/− versus WT; PA data not shown		

References	Mouse strain, sex	Model description/background/rationale	Basal PPI	Effects of drugs or manipulations typically used to induce PPI-deficits	Effects of (presumed) antipsychotics/other treatments
		KALRN −/− have decreased spine density (this paper)			
		Oxidative stress			
Benoit et al.(2010)	QR2 KO, M	QR2 enhances production of quinine and reactive oxygen species (ROS) and is upregulated in cognitively impaired aged rats; polymorphism in QR2 promoter region weakly associated with SZ	ØPPI in −/− versus WT; PA data not shown		
Cole et al.(2011)	GCLM KO, M	GCLM is rate-limiting enzyme in glutathione (GSH) synthesis; GSH defends against oxidative stress	ØPPI & ØPA in −/− versus WT		
		Metallothionines			
Koumura et al.(2009)	MT3 KO, M	Metallothionines (MTs) bind zinc and other metals and are neuroprotective in some models	↓PPI & ØPA in −/− versus WT		
		Neurodevelopmental genes (other)			
Willi et al.(2010)	Nogo-A KO, M	Nogo-A inhibits growth during development and in adulthood and thus may be involved in neurodev and neural plasticity; some evidence of pathology in SZ	↓PPI & ØPA in −/− versus WT		
Takata et al.(2010)	XBP1 KO, M	XBP1 gene encodes transcription factor in the ER unfolded protein response; involved in brain development and potentially pathogenesis of bipolar disorder and depression	↑PPI & ØPA in +/− versus WT		
		Glycoproteins			
Sakatani et al.(2009)	RAGE KO, M	RAGE is a receptor for multiple ligands including Aβ, HMGB1, and S100B, which contribute to the pathology of AD, epilepsy, and ischemia	↑PPI in −/− versus WT ↑PA in −/− versus WT at low sound pressure levels (70–100 dB); ↓PA in −/− versus WT at 120 dB		
Fukuda et al.(2011)	Fut8 KO, M	α1,6 fucosyltransferase (Fut8)[2] transfers fucose from a GDP-fucose to position 6 of N-acetylglucosamine to form N-linked oligosaccharides of glycoproteins. Fucosylated glycoproteins widely distributed in brain	↓PPI & ØPA in −/− versus +/− & WT	*After restraint stress* ↓PPI & ØPA in +/− versus WT	
		Sex hormones			

References	Mouse strain, sex	Model description/background/rationale	Basal PPI	Effects of drugs or manipulations typically used to induce PPI-deficits	Effects of (presumed) antipsychotics/other treatments
Chavez et al.(2009)	ArKO, M, F	Gender differences in the age of onset, severity, and response to treatment in SZ. Second increase in SZ incidence in older age for women when estrogen levels decline. Thus, estrogen may be neuroprotective against development of SZ. Aromatase (Ar) converts androgens to estrogens	ØPPI in −/− versus WT	AMP ↓PPI in −/− & WT (↓PPI slightly attenuated in F −/−), ↓PA in −/− & WT *Apo*: ↓PPI in −/− & WT (↓PPI slightly attenuated in F −/−), ↓ PA in −/− & WT *MK801*: ↓PPI & ↑PA in −/− & WT	

Abbreviations 5-HT serotonin, *AAV* adeno-associated virus, *A*β amyloid β- peptide, *ACE* angiotensin converting enzyme, *ACH* acetylcholine (receptor), *AD* Alzheimer's disease, *ADX* adrenalectomy, *AIL* advanced intercross line, *AMP* amphetamine, *AMY* amygdala, *APD* antipsychotic drug, *APP* amyloid precursor protein, *ARIP* aripiprazole, *APO* apomorphine, *AT* angiotensin, *BAC* bacterial artificial chromosome, *BACE* β-site APP cleaving enzyme, *BD* bipolar disorder, *BG* background, *CaMKIV* calcium-calmodulin-dependent protein kinase IV, *cAMP* cyclic adenosine monophosphate, *Ckr* chakragati, *CLO* clozapine, *CNS* central nervous system, *COC* cocaine, *COMT* catechol-O-methyltransferase, *CORT* corticosterone, *CRF* corticotropin releasing factor, *CTR* controls, *CTX* cortex, *DA* dopamine (receptor), *DAT* dopamine transporter, *dB* decibel, *DCC* deleted in colorectal cancer, *DIAZ* diazepam, *DIZ* dizocilpine, *DN* dominant-negative, *DDO* D-aspartate oxidase, *E* embryonic day, *EE* environmental enrichment, *EGF* epidermal growth factor, *ENU* N-ethyl-N-nitrosourea, *f* frontal, *F* female, *FABP* fatty acid binding protein, *FGF* fibroblast growth factor, *Fmr1* fragile × mental retardation 1 gene, *FMRP* fragile × mental retardation protein, *FXS* fragile × Syndrome, *GLAST* glutamate and aspartate transporter, *GLU* glutamate, *GluR* glutamate receptor, *GLUT* glucose transporter, *GR* glucocorticoid receptor, *GRIP* glutamate receptor interacting protein, *GSK* glycogen synthase kinase, *GWAS* genome wide association studies, *HAL* haloperidol, *HD* Huntington's disease, *HPC* hippocampus, *IC* imprinted cluster, *IL* interleukin, *ISI* interstimulus interval, *KI* knock-in, *KO* knock-out, *M* male, *m* metabotropic, *MDB* methyl-CpG binding protein, *mo* month, *NIC* nicotine, *MPEP* 2-methyl-6-(phenylethylyn)-pyridine hydrocholoride, *METH* metamphetamine, *Mgat* N-acetylglucosaminyltransferase, *NAA* N-acetyl-aspartate, *NAAG* N-acetylalpha L-aspartyl-L-glutamate, *NAC* nucleus accumbens, *NCAM* neural cell adhesion molecule, *NIS* nisoxetine, *nNOS* neuronal nitric oxide synthase, *NO* nitric oxide, *NPS* neuropeptide S (receptor), *NPY* neuropeptide Y, *NR* NMDA receptor subunit, *NRG* neuregulin, *NRL* neuroligin, *ns* not significant(ly), *NSE* neuron-specific enolase, *NT* neurotensin, *OE* overexpressor, *OXO* oxotremorine, *PA* magnitude of response to pulse alone, *PACAP* pituitary adenylate-cyclase-activating polypeptide, *PD* Parkinson's disease, *PDE* phosphodiesterase, *PET-1* plasmocytoma expressed transcript-1, *PND* postnatal day, *PLC* phospholipase C, *PNS* prenatal stress, poly I:C polyinosinic: polycytidylic acid, *PP* prepulse, *PPI* prepulse inhibition of startle, *PPP* prepulse potentiation, *PS1* presinilin1, *PWS* Prader–Willi syndrome, *QTL* quantitative trait locus, *QUET* quetiapine, *RAC* raclopride, *RAGE* receptor for advanced glycation end-products, *RasGAP* Ras GTPase-activating protein, *RE* renin-enhancer, *RIS* risperidone, *SCOP* scopolamine, *SI* social isolation, *SNP* single nucleotide polymorphism, *SOCS* suppressor of cytokine signaling; *SREB* superconserved receptor expressed in brain; *STR* striatum, *SYN* synapsin, *SynGAP* synaptic GTP-ase-activating protein, *SZ* schizophrenia, *TAAR* trace amine-associated receptor, *TG* transgenic, TGF-β transforming growth factor beta, *TK* typosine kinase, *TMS* transcranial magnetic stimulation, *V1b* vasopressin receptor 1b, *WT* wild-type

↓ decreased, ↑ increased, Øunchanged, −/− homozygous mice, +/− heterozygous mice

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Table 4

Genetically engineered model organisms (ca. 07/01/2007-06/28/2011) based on genes related to: *models for specific disorders*

References	Mouse strain, sex	Model description/background/rationale	Basal PPI	Effects of drugs or manipulations typically used to induce PPI-deficits	Effects of (presumed) antipsychotics/other treatments
		Alzheimer's disease			
Dejaegere et al. (2008)	Alpha 1B/C γ-secretase KO	γ-secretases have been implicated in the cleavage of membrane proteins incl. APP, & NRG (a SZ vulnerability gene) & in NOTCH signaling	↓PPI (most pronounced at high PA intensities) & ØPA in −/− versus WT		*HAL:* (↑PPI & ØPA in −/− & WT) *CLO:* (↑PPI in −/−; ØPPI in WT; ØPA in −/− & WT)
Gruart et al. (2008)	APP, PS1, APP+PS1 TG, M	Neuropathological changes in brain regions regulating PPI may occur in AD models & may affect PPI	↓PPI in 18 mo old WT, APP KO, PS1 KO & APP+PS1 TG versus 3 mo old WT. Most pronounced ↓PPI in 18 mo APP+PS1 TG. PA data not shown		
Tsujimura et al. (2008)	KF-1 KO, M	KF-1 gene increased in AD patients; localized in hippocampus, cerebellum; modulates protein levels as a ubiquitin ligase; increased in frontal ctx after chronic antidepressant treatment, electroconvulsive therapy, and TMS	↑PPI in −/− versus WT; ↓PA in −/− versus WT		
Takeuchi et al. (2011)	P301S Tg, M	Tau, a microtubule-associated protein, can cause cell death and is associated with AD and other neurodegenerative diseases. FTDP17 (frontotemporal dementia and PD linked to chromosome 17) is linked to a point mutation in tau (P301S)	↑PPI & ↓PA at 120 dB only in Tg versus WT		
		Autism			
Allan et al. (2008)	MDB1 KO, M & F	Via DNA methylation, MDB mediate epigenetic gene regulation, which has been linked to neurodevelopmental disorders, including autism	↓PPI & ØPA in −/− versus WT		
Chadman et al. (2008)	NL3 KI, M & F	Neuroligin-3 (NL3) is a cell adhesion molecule involved in synapse development & implicated in autism; "knock in" of point mutation identified in autism	ØPPI in KI versus WT; ↓PA in KI versus WT		
Radyushkin et al. (2009)	NL3 KO, M	Point mutations in neuroligin-3 are associated with autism	ØPPI & ØPA in −/− versus WT		
Moy et al. (2009)	NRCAM KO, M & F	NRCAM identified as a candidate gene for autism; involved in cell-cell interactions during brain development and thus affect axonal guidance and neural circuit development	↓PPI in −/− versus WT (M only; ØPPI in F); ØPA in −/− versus WT		
DeLorey et al. (2011)	GABRB3 KO, M & F	GABRB3 gene associated with autism	ØPPI (F) & ↑PPI (M) in +/− versus		

References	Mouse strain, sex	Model description/background/rationale	Basal PPI	Effects of drugs or manipulations typically used to induce PPI-deficits	Effects of (presumed) antipsychotics/other treatments
			WT; ↓PA (M & F) in +/− versus WT		
Mejias et al. (2011)	GRIP1/2 DKO (double KO, Grip1 flox/KO, Grip2 KO/KO)	GRIP1 scaffolding protein that interacts with GLU2/3 via PDZ domains 4-6. SNP in PDZ4-6 domain and 5 missense variants identified in ASD (this paper)	↓PPI in −/− versus WT mice		
		Fragile X-syndrome (FXS)			
de Vrij et al. (2008)	FMR1 KO	FXS involves mental retardation & is caused by the absence of FMRP. PPI is reduced in FXS patients	↓PPI at most PP intensities in −/− versus WT		MPEP (mGluR5 antagonist; ↑PPI in −/− & WT)
Paylor et al. (2008)	FMR1 KO, FMR1 KO with a yeast artificial chromosome containing human FMR1 gene, M		↑PPI & ↓PA (trend) in −/− versus WT		Addition of human FMR1 gene normalized, i.e. ↓PPI & ↑PA in FMR1 KO to WT levels, & ↓PPI & ØPA in WT
Baker et al. (2010)	FMR1 KO, M & F	Background strain may affect behavioral phenotype in FMR1 KO mice; bred to albino C57BL/6J-Tyr(c-Brd) background	↑PPI & ↓PA in −/− versus WT (both sexes)		
Levenga et al. (2011)	FMR1 KO, M	FMRP involved in translation of mRNA at the synapse, downstream from mGlu5 signaling	↓PPI in −/− versus WT; PA data not reported (startle measured via eyeblink)		*AFQ056, mGluR5 antagonist*: ↑PPI in −/−; ØPPI in WT
Veeraragavan et al. (2011)	FMR1 KO, M	Increased M1 muscarinic signaling in FMR1 KO mice	ØPPI & ØPA in −/− versus WT		*Dicyclomine*: ØPPI & ØPA in −/− or WT
Thomas et al. (2011a)	mG1.FMR1 (mGlu1 HZ + FMR1 KO); mG5.FMR1 (mGlu5 HZ + FMR1 KO); FMR1 KO	FMR1 may increase signaling through Group 1 mGluRs (mGlu1, mGlu5)	↑PPI & ↓PA in FMR1−/− & mG5.FMR1 versus WT; ↑PPI & ↓PA in FMR1−/− & mG1.FMR1 versus WT		
Thomas et al. (2011b)	FMR1 KO, M & F	Group 1 mGluRs may be pharmacological target in Fragile X	↓PA & ØPPI (trend for predicted ↑) in −/− versus WT	*JNJ (mGlu1 antagonist)*: ↓PPI in WT, ØPPI in −/−; ØPA in −/− & WT *MPEP (mGlu5 antagonist)*: ØPPI & ØPA in −/− & WT	
		Huntington's disease			

References	Mouse strain, sex	Model description/background/rationale	Basal PPI	Effects of drugs or manipulations typically used to induce PPI-deficits	Effects of (presumed) antipsychotics/other treatments
Menalled et al. (2009)	R6/2 TG, R6/2B TG, YAC128 TG, YAC128B TG, BACHD TG, HDH^{Q111} KI, M & F	HD results from a known genetic CAG repeat mutation; ↓PPI in HD patients; HD mutant mice show varying degrees of neuropathology and behavioral abnormalities; comparison controlling for many factors including sex, background strain, husbandry, and handling	*R6/2*: ↓PPI in TG versus WT beginning at 12 wks; ↓PA *R6/2B*: ↓PPI in TG versus WT *BACHD*: ↓PPI beginning at 24 wks; ØPA *YAC128B*: ↓PPI at 54 wks; ØPA *YAC128*: ØPPI; ØPA HDH^{Q111} KI: ØPPI; ØPA		
Brooks et al. (2010)	Hdh$^{(CAG)150}$ KI, M & F	Longitudinal characterization of KI mouse carrying 150 CAG repeats on the mouse Htt locus	↓PPI & ↓PA in KI versus WT		
Brooks et al. (2011)	R6/1 TG, M & F	R6/1 TG mouse contains ~ 115 CAG repeats on exon 1 of the HD gene. Characterization of R6/1 TG mice on C57BL/6 background is needed	↓PPI & ↓PA in TG versus WT		
Pietropaolo et al. (2011)	R6/1 TG, M & F	Investigate neuropsychiatric symptoms in premotor stage of pathology	ØPPI & ØPA in TG versus WT		
		Hearing disorders			
Allen et al. (2008)	Kv1.1 KO	PPI in rodents is a powerful means to identify hearing deficits. The role of Kv1.1 channels in PPI gap detection paradigms was assessed	↓PPI (for long gaps only)		
		22q11 deletion & duplication syndromes			
Suzuki et al. (2009b)	SEPT5 (Septin5) KO, M	22q11.2 microdeletions result in cognitive & behavioral abnormalities and are associated with SZ and autism; SEPT5 gene located on 200kb region spanning the deletion	↑PPI & ØPA in −/− versus WT		
Stark et al. (2009)	*BAC Tg-1*: Overexpress Prodh & Vpreb2 *BAC Tg-2*: overexpress Zdhhc8, Ranbp1, Htf9c, T10, Arvcf, & COMT	22q11.2 microduplications are also associated with behavioral problems and learning disabilities; gain of function mutations can also be informative for the deletion syndrome	*Tg-1*: ↑PPI & ØPA in Tg-1 versus WT *Tg-2*: ØPPI & ØPA in Tg-2 versus WT		
Suzuki et al. (2009a)	*BAC Tg, M*: overexpress 190 kb segment of 22q11.2 including TXNRD2, COMT, ARVCF	22q11.2 is a hotspot for CNVs. 97% of children with 22q11.2 duplications show cognitive deficits	ØPPI & ØPA in Tg versus WT		
		Down syndrome			

References	Mouse strain, sex	Model description/background/rationale	Basal PPI	Effects of drugs or manipulations typically used to induce PPI-deficits	Effects of (presumed) antipsychotics/other treatments
Ortiz-Abalia et al. (2008)	TG DyrK1A overexpressors, M	DyrK1A overexpression has been implicated in Down Syndrome	↓PPI at higher PP intensities in TG versus WT (trend only); PA not shown		*Intrastriatal infusion of AAV iRNA against Dyrk1A*: PP intensity-dependent ↑PPI in TG treated with functional versus scrambled viral vectors & pre versus post-treatment with functional vector; PA not shown
		Glycosilation IIa congenital disorders			
Soleimani et al. (2008)	Mgat5 KO, M & F	Mgat5 is involed in glycosylation of cell surface glycoproteins, including receptors & transporters. Abundant in the CNS	ØPPI & PA in −/− versus WT; ↑PA in M versus F (main effect)		
		Prader-Willi syndrome			
Relkovic et al. (2010)	PWS-IC (+/−), M & F	Prader-Willi Syndrome (PWS) neurodevelopmental disorder resulting from deletion of paternally expressed imprinted genes of chromosome 15q11–q13, a region also implicated in autism and SZ	↓PPI & ↑PA in +/− versus WT in M & F (only at P105 in M)		

Abbreviations: *5-HT* serotonin, *AAV* adeno-associated virus, *A*β amyloid β- peptide, *ACE* angiotensin converting enzyme, *ACH* acetylcholine (receptor), *AD* Alzheimer's disease, *ADX* adrenalectomy, *AIL* advanced intercross line, *AMP* amphetamine, *AMY* amygdala, *APD* antipsychotic drug, *APP* amyloid precursor protein, *ARIP* aripiprazole, *APO* apomorphine, *AT* angiotensin, *BAC* bacterial artificial chromosome, *BACE* β-site APP cleaving enzyme, *BD* bipolar disorder, *BG* background, *CaMKIV* calcium-calmodulin-dependent protein kinase IV, *cAMP* cyclic adenosine monophosphate, *Ckr* chakragati, *CLO* clozapine, *CNS* central nervous system, *COC* cocaine, *COMT* catechol-O-methyltransferase, *CORT* corticosterone, *CRF* corticotropin releasing factor, *CTR* controls, *CTX* cortex, *DA* dopamine (receptor), *DAT* dopamine transporter, *dB* decibel, *DCC* deleted in colorectal cancer, *DIAZ* diazepam, *DIZ* dizocilpine, *DN* dominant-negative, *DDO* D-aspartate oxidase, *E* embryonic day, *EE* environmental enrichment, *EGF* epidermal growth factor, *ENU* N-ethyl-N-nitrosourea, *f* frontal, *F* female, *FABP* fatty acid binding protein, *FGF* fibroblast growth factor, *Fmr1* fragile × mental retardation 1 gene, *FMRP* fragile × mental retardation protein, *FXS* fragile × Syndrome, *GLAST* glutamate and aspartate transporter, *GLU* glutamate, *GluR* glutamate receptor, *GLUT* glucose transporter, *GR* glucocorticoid receptor, *GRIP* glutamate receptor interacting protein, *GSK* glycogen synthase kinase, *GWAS* genome wide association studies, *HAL* haloperidol, *HD* Huntington's disease, *HPC* hippocampus, *IC* imprinted cluster, *IL* interleukin, *ISI* interstimulus interval, *KI* knock-in, *KO* knock-out, *M* male, *m* metabotropic, *MDB* methyl-CpG binding protein, *mo* month, *NIC* nicotine, *MPEP* 2-methyl-6-(phenylethylyn)-pyridine hydrocholoride, *METH* metamphetamine, *Mgat* N-acetylglucosaminyltransferase, *NAA* N-acetyl-aspartate, *NAAG* N-acetylalpha L-aspartyl-L-glutamate, *NAC* nucleus accumbens, *NCAM* neural cell adhesion molecule, *NIS* nisoxetine, *nNOS* neuronal nitric oxide synthase, *NO* nitric oxide, *NPS* neuropeptide S (receptor), *NPY* neuropeptide Y, *NR* NMDA receptor subunit, *NRG* neuregulin, *NRL* neuroligin, *ns* not significant(ly), *NSE* neuron-specific enolase, *NT* neurotensin, *OE* overexpressor, *OXO* oxotremorine, *PA* magnitude of response to pulse alone, *PACAP* pituitary adenylate-cyclase-activating polypeptide, *PD* Parkinson's disease, *PDE* phosphodiesterase, *PET-1* plasmocytoma expressed transcript-1, *PND* postnatal day, *PLC* phospholipase C, *PNS* prenatal stress, poly I:C polyinosinic: polycytidylic acid, *PP* prepulse, *PPI* prepulse inhibition of startle, *PPP* prepulse potentiation, *PS1* presinilin1, *PWS* Prader–Willi syndrome, *QTL* quantitative trait locus, *QUET* quetiapine, *RAC* raclopride, *RAGE* receptor for advanced glycation end-products, *RasGAP* Ras GTPase-activating protein, *RE* renin-enhancer, *RIS* risperidone, *SCOP* scopolamine, *SI* social isolation, *SNP* single nucleotide polymorphism, *SOCS* suppressor of cytokine signaling; *SREB* superconserved receptor expressed in brain; *STR* striatum, *SYN* synapsin, *SynGAP* synaptic GTP-ase-activating protein, *SZ* schizophrenia, *TAAR* trace amine-associated receptor, *TG* transgenic, TGF-β transforming growth factor beta, *TK* typosine kinase, *TMS* transcranial magnetic stimulation, *V1b* vasopressin receptor 1b, *WT* wild-type

↓ decreased, ↑ increased, Ø unchanged, −/− homozygous mice, +/− heterozygous mice

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Table 5

Phenotype-based approaches

References	Mouse strain, sex	Model description/ background/rationale	Basal PPI	Effects of drugs or manipulations typically used to induce PPI-deficits	Effects of (presumed) antipsychotics/other treatments
		QTL approaches			
Cook et al. (2007)	ENU-mutagenesis-induced variants	Genome-wide screening for neurobehavioral phenotypes, including PPI	2 PPI mutants with ↓PPI		
Watanabe et al. (2007)	F2 mice from C57BL/6 × C3H/HE crosses, M, & F	Screening for PPI and startle phenotypes	6 loci for PPI, 6 for startle and four for startle latency were identified, incl. FABP7 (linked to NMDAR function (↓PPI & ↓PA latency)		
Hitzemann et al. (2008)	C57BL/6J, DBA/2J, BALBc/J and LP/J crosses, M & F	Selective breeding for high and low PPI	ØPPI & PA in M versus F and no correlation between PPI & PA initially. Breeding line × generation effects on PPI (low vs. high PPI line) after five generations. No line × generation effects on PA, but ↑PA in low PPI line versus ↓PA in high PPI line (main effect only). QTL on chromosomes 11 & 16 in low PPI versus high PPI line	METH (Line × dose interaction. ↓PPI in high PPI line, but ØPPI in low PPI line at highest METH dose). DIZ (↓PPI; main effect of dose only, no line × dose interaction)	HAL(↑PPI; main effect of dose only, no line × dose interaction)
Torkamanzehi et al. (2008)	A/J, C57Bl6/J and congenic crosses thereof, M	Screening for PPI and PA phenotypes using light prepulses and tactile startle pulses	Comparable PPI, but not PA in parental strains. Significant variation for congenic strains for PA for both BG and for PPI in C57Bl6 BG strains. Common markers with acoustic PA, but not acoustic PPI from previous study (Joober et al. 2002)		
Samocha et al. (2010)	LG/J × SM/J F_2 cross & F_{34} advanced intercross line (AIL), M, F	PPI and PA phenotyping followed by QTL in F_2 generation and genotyped F_{34} line at 3000 SNP markers	QTLs found at chromosome 12 for all PP intensities; QTLs for PP6 & PP12 on chromosome 7; QTLs on chromosomes 7 & 17 for startle response; QTLs on chromosome 4 for startle habituation; AIL mice reduced size of some QTLs to less than 5 cm		
		Insertional mutagenesis			
Verma et al. (2008)	Ckr mouse, M, F	*Ckr* serendipidous mutation resulted in mouse with abnormal circling behavior	↓PPI (modest) at all PP intensities in Ckr versus (+/− & WT); ØPA in Ckr versus −/+ or WT		CLO (↑PPI in Ckr; ØPPI in WT; RIS (ØPPI in Ckr & WT), HAL (ØPPI in Ckr & WT); PA data not shown

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