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Sensorimotor Gating Deficits in "Two-Hit" Models of Schizophrenia Risk Factors

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Abstract

Genetic and environmental models of neuropsychiatric disease have grown exponentially over the last 20 years. One measure that is often used to evaluate the translational relevance of these models to human neuropsychiatric disease is prepulse inhibition of startle (PPI), an operational measure of sensorimotor gating. Deficient PPI characterizes several neuropsychiatric disorders but has been most extensively studied in schizophrenia. It has become a useful tool in translational neuropharmacological and molecular genetics studies because it can be measured across species using almost the same experimental parameters. Although initial studies of PPI in rodents were pharmacological because of the robust predictive validity of PPI for antipsychotic efficacy, more recently, PPI has become standard common behavioral measures used in genetic and neurodevelopmental models of schizophrenia. Here we review "two hit" models of schizophrenia and discuss the utility of PPI as a tool in phenotyping these models of relevant risk factors. In the review, we consider approaches to rodent models of genetic and neurodevelopmental risk factors and selectively review "two hit" models of gene × environment and environment × environment interactions in which PPI has been measured.

Keywords

behavior; development; prepulse inhibition; schizophrenia; genetic; risk factor; double hit; sensorimotor gating

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1. Introduction: Utility of Prepulse Inhibition in Models Relevant to Schizophrenia

Sensorimotor gating occurs when a motor responses is gated by a sensory event. One form of sensorimotor gating that has been studied at multiple levels of biology, from its cellular mechanisms (Frost et al., 2003; Nusbaum and Contreras, 2004; Rose and Scott, 2003) to its relationship to neuropsychiatric disease (Braff, 2010, 2011; Swerdlow et al., 2008), is prepulse inhibition (PPI) of startle. PPI occurs when a weak, subthreshold stimulus presented 30–500 ms prior to an intense startling stimulus inhibits the startle response (Graham, 1975; Hoffman and Ison, 1980). The circuitry of PPI has been studied most extensively in rodents and involves role of cortico-striatal-pedunculo-pontine (CSPP) circuitry in which limbic and descending pontine projections modulate the ability of the prepulse to inhibit the startle response, which occurs at the level of the pons (Swerdlow et al., 2001a; Swerdlow et al., 2008). Thus, PPI provides an operational measure of sensorimotor gating and may indicate the integrity of the underlying neural circuitry subserving sensorimotor gating mechanisms. PPI is an integral part of human psychophysiological studies of neuropsychiatric disease and is amenable to neuroscience-based inquiry of deficits in functional domains. Indeed, in the Research Domain Criteria (RDoC) outlined by the National Institute of Mental Health, PPI is considered part of the "Auditory Perception" construct in the cognitive domain. In humans, startle to acoustic or tactile stimuli is most often measured from the eye blink response (Braff et al., 1992; Fridlund and Cacioppo, 1986; Kumari et al., 2003; Neuner et al., 2010; Swerdlow et al., 2001b). PPI deficits were first observed in schizophrenia patients (for review see Braff et al., 2001; Swerdlow et al., 2014; Swerdlow et al., 2008), but are also apparent in their unaffected first degree relatives (Cadenhead et al., 2000) as well as patients with schizotypal personality disorder (Cadenhead et al., 1993). A recent large, multi-site study reported PPI deficits in schizophrenia patients, corroborating the more than 40 single-site studies published to date (Swerdlow et al., 2014). PPI deficits, however, are not unique to schizophrenia and are also observed in several other neuropsychiatric disorders (Kohl et al., 2013), including Obsessive-Compulsive Disorder (Ahmari et al., 2012; Ahmari et al., 2016; Hoenig et al., 2005; Swerdlow et al., 1993), Tourette's syndrome (Buse et al., 2016; Castellanos et al., 1996; Swerdlow et al., 2001b), Huntington's disease (Swerdlow et al., 1995; Valls-Sole et al., 2004), manic bipolar patients (Perry et al., 2001), Panic Disorder (Ludewig et al., 2002), Fragile × syndrome (Frankland et al., 2004; Hessl et al., 2009), adults with autism (Perry et al., 2007), Asperger's Syndrome (McAlonan et al., 2002), 22q11 Syndrome (Sobin et al., 2005), nocturnal enuresis (Ornitz et al., 1992), and Kleinfelter Syndrome (van Rijn et al., 2011). Thus, PPI deficits are observed across many neuropsychiatric disorders but have been the most widely replicated in schizophrenia patients (Braff et al., 2001; Kumari et al., 2008; Ludewig et al., 2003; Mackeprang et al., 2002; Swerdlow et al., 2008).

PPI has been a useful behavioral phenotype to consider in genetic mouse models relevant to schizophrenia and other neuropsychiatric diseases (Powell et al., 2012). Additionally, because PPI measures basic information processing and can be quantified in multiple species, it is a useful tool for understanding the biology of putative risk genes. Indeed, over the last 20 years a large number of genetic mouse models have been tested for differences in

PPI. These studies indicate that PPI can be either increased or decreased by a wide variety genes involved in neural development, neurotransmitter function, or basic cellular processes (Powell et al. 2009; Powell et al. 2012). Our recent review provided an update on mutant mouse models in which PPI was measured as a phenotype with comprehensive tables detailing PPI across a wide variety of mutant models and its pharmacological modulation, where appropriate (Powell et al., 2012). PPI has also proven to be a useful tool in evaluating the impact of environmental risk factors during development, which is covered briefly in Section 3.

Previous reviews summarized schizophrenia candidate genes (Arguello and Gogos, 2010; Arguello and Gogos, 2011; O'Tuathaigh and Waddington, 2015), while other reviews focused specifically on PPI, summarizing genetic mutants, strain differences, and the pharmacology of PPI in mice (Geyer et al., 2002; Powell et al., 2012; Powell et al., 2009; Swerdlow et al., 2008; van den Buuse, 2010), as well as recent reviews on models of gene × environment interactions (Ayhan et al., 2016; Moran et al., 2016). The etiology of schizophrenia is multifaceted and likely involves a convergence of both genetic and environmental risk factors (Cannon et al., 2003; Gottesman, 1991; Uher, 2014). Thus, experimental models evaluating gene-environment interactions are particularly informative for schizophrenia. In this review, we summarize approaches to rodent models of genetic and neurodevelopmental risk factors and selectively review "two hit" models of gene × environment and environment × environment interactions in which PPI has been measured. The review highlights approaches to combined risk factors for schizophrenia that have used PPI as a behavioral endpoint and discusses caveats of, and future directions for, double hit models.

2. Genetic Landscape of Schizophrenia

2.1 Approaches to genetic discoveries

The two primary approaches to understanding the genetics of neuropsychiatric disease are the common disease / common allele approach (CDCA) and the common disease / rare allele approach (CDRA) (Arguello and Gogos, 2011). Candidate gene or unbiased genome-wide association studies (GWAS) focus on common genetic variants (>5% allele frequency); whereas, the CDRA approach focuses on the hypothesis that rare variants with high penetrance can cause common disease (Arguello and Gogos, 2011). Schizophrenia and other major neuropsychiatric and neurodevelopmental conditions are likely a combination of risk from both common and rare variants.

The recent Psychiatric Genomics Consortium (PGC) genome-wide association study (GWAS) of schizophrenia (Consortium, 2014) identified 108 genetic loci associated with schizophrenia. Some of the most notable findings in the PGC are loci containing genes for G protein coupled receptor signaling, glutamate neurotransmission, neuronal calcium signaling, synaptic function and plasticity, other neuronal ion channels, and neurodevelopment (Consortium, 2014). Because these associations imply the existence of one or more risk variants at the locus rather than a specific gene, it is premature to discuss in depth the role of any specific genes at these loci until there is a more complete understanding of the risk variants and whether the variants are functional. As the basic

biology of the identified loci begins to be investigated, there will certainly be many mouse mutants created to target those genes. One strategy for using the PGC GWAS data for neuroscience drug discovery put forth by Schubert and colleagues, is to prioritize gene targets based on knowledge of gene function and functional variants to identify putatively causal genes, and annotate these putatively causal genes with information on mRNA expression, *de novo* mutations, disease-associated rare mutations, and literature knowledge to determine targets for novel drug discovery (Schubert et al., 2014). A similar strategy could be taken by molecular biologists creating novel mouse mutants for basic biological interrogations of target genes. Another interesting finding emerging from large-scale GWAS studies across psychiatric disorders is the large degree of genetic overlap between schizophrenia and both autism spectrum disorder (ASD) and bipolar disorder, suggesting shared disease pathways or common risk. Thus, mouse models manipulating these genes should be considered a more general risk factor for multiple neurodevelopmental and/or neuropsychiatric disorders.

2.2 Genetics of PPI as an endophenotype

A complementary approach to large-scale GWAS or copy number variant (CNV) studies of schizophrenia are genetic studies of endophenotypes, which assume that the endophenotypemore proximal to the biological function of disrupted genes and/or be more easily and reliably quantified. Hence, psychophysiological processes such as PPI, have been used as endophenotypes in schizophrenia genetic studies (Braff et al., 2007; Greenwood et al., 2011; Greenwood et al., 2012; Greenwood et al., 2013) based on meeting criteria for a viable endophenotype (e.g. heritable, easily measured, good test-retest reliability; (Turetsky et al., 2007). PPI heritability has been estimated at 32%, which is similar to the 31% and 44% schizophrenia heritability estimates for nuclear and extended families, respectively, suggesting similar heritabilities for the disease and the endophenotype (Greenwood et al., 2007; Light et al., 2014).

Candidate gene studies indicated that 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) are associated with PPI. In more recent studies of multiple SNPs using much larger sample sizes, however, only a few of these associations remained. In the larger, family-based COGS (Consortium on the Genetics of Schizophrenia) dataset, SNPs for CHRNA7, NCAM1, COMT, GRID2, CAMK2A were the most strongly associated with PPI, and NOS1AP, GRIK3, NRG1, GRIN3A, and DBH moderately associated with PPI (Greenwood et al., 2011). In a follow-up study based on non-familial samples from UCSD (Greenwood et al., 2012) only GRID2 achieved significance at more stringent significance levels. Other genes including GRIK3, CTNNA2, SLC6A3, SLC1A2, and GRIN2A were modestly associated with PPI. Across the endophenotypes studied in the UCSD and COGS samples, GRID2 and GRIK3 were significantly associated with PPI in both studies, strengthening the potential for these two genes to be promising genetic hits. The other gene that appeared across two separate studies was SLC6A3 (dopamine transporter gene). In addition to the modest association with PPI in the Greenwood et al. (2012) study, a genome-wide linkage analysis of the COGS sample suggested linkage (LOD score >2.2) for PPI on chromosome 5p15, a “gene dense” region that contains SLC6A3

(Greenwood et al., 2013), indicating that the dopamine transporter may be an additional gene of interest for follow up studies. Whether this endophenotype approach is more useful than genetic studies based on disease diagnosis is heavily debated in psychiatric genetics, but it is certainly complementary to GWAS studies of disease and may offer useful information regarding biological processes that cut across psychiatric diagnoses (Cuthbert and Insel, 2013).

2.3. Mutant Mouse Models: Where to go from here?

McCarroll et al. 2014 argue that a new "biological playbook" needs to be written to address the new genetic discoveries emerging from unbiased genome-wide studies (McCarroll et al., 2014). The question for molecular biologists and basic neuroscientists is - what potential genetic "hits" from association studies are plausible targets for follow-up biological studies? Since the genes identified in the PGC study are common variants with small effect, biological models would likely need to manipulate multiple genes to see a biologically relevant effect (Need and Goldstein, 2014). Biological interrogation of the genetic regions identified through GWAS are hindered by: (1) lack of clear functional effects of the identified SNPs, (2) the likelihood that multiple genes interact to produce the full manifestation of disease, (3) the identified risk alleles can be distal to the causative gene, and (4) the likely possibility that common variants modify disease risk produced primarily by rare variants (Arguello and Gogos, 2011). Thus, the ability to target specific genes or multiple genes in rodent models becomes daunting. Need & Goldstein (2014) suggest that a better approach may be to focus basic biological and model organism studies on more highly penetrant rare mutations such as chromosomal deletions or duplications identified by CNV analyses (Need and Goldstein, 2014), while continuing to interrogate the function of the 108 identified loci from the PGC study.

3. Neurodevelopmental models of schizophrenia

3.1. Neurodevelopmental risk factors

There is increasing evidence that schizophrenia has its roots in disrupted brain development due to both genetic and environmental risk factors, leading to psychosis emergence in adolescence and early adulthood (Cannon et al., 2003; Murray et al., 2002; Rapoport et al., 2012). Environmental risk factors are evident throughout development and include prenatal and perinatal risk factors, psychological risk factors in early life and adolescence, and exposure to drugs of abuse or trauma in adulthood. Several general factors such as season of birth (late winter/early spring) (Boyd et al. 1986; Machon et al. 1983; Mino & Oshima 2006; Torrey et al. 1997) and social factors such as urbanicity, immigrant status, and social isolation are associated with increased schizophrenia risk (Cannon et al., 2008; Dean et al., 2003; Marcelis et al., 1998). More specific risk factors include prenatal exposure to inflammation or birth complications, as well as adolescent exposure to drugs of abuse. Prior to discussing studies evaluating these risk factors in the context of gene × environment or environment × environment interactions, we first briefly review the evidence for the associated risk with schizophrenia. We focus on risk factors for schizophrenia because epidemiological studies of disease risk are what have produced candidate risk factors in model organisms in which PPI was measured.

3.2. Prenatal, perinatal, and early postnatal risk factors

Early life exposures to adverse environmental factors, either *in utero* or during the perinatal period, increase the risk of schizophrenia and include maternal stress, maternal malnutrition, immune activation or infections, or obstetric complications (Lewis and Levitt, 2002). PPI is a behavioral measure that has been extensively studied in many of these neurodevelopmental models as we have previously reviewed (Powell, 2010).

Epidemiological studies suggest an increased incidence of schizophrenia after exposure to viral or bacterial infections during early to mid gestation (reviewed in Brown and Susser, 2002; Fatemi and Folsom, 2009; Patterson, 2009; but see also Selten et al., 1999), with links being found between influenza (Mednick et al., 1988; O'Callaghan et al., 1991), bacterial infections (Sorensen et al., 2009), and also toxoplasmosis (Brown et al., 2005). These epidemiological studies have been supported by serological evidence of increased levels of gestational influenza infection (Brown et al., 2004a) and increased maternal levels of cytokines such as TNF-alpha (Buka et al., 2001) and IL-8 (Brown et al., 2004b) during pregnancy in mothers of individuals with schizophrenia. Animal studies have investigated the effects of maternal challenges with viral infection (e.g. influenza virus (Shi et al., 2003), immune activating agents such as the viral mimic polyriboinosinic-polyribocytidilic acid (PolyI:C), and bacterial endotoxin lipopolysaccharide (LPS) (for more thorough reviews see Estes and McAllister, 2016; Meyer, 2014; Meyer and Feldon, 2009a; Meyer and Feldon, 2009b; Patterson, 2009; Powell, 2010).

Prenatal nutritional deficiency has also been shown to increases the risk of schizophrenia (Brown and Susser, 2008; Susser et al., 1996; Xu et al., 2009). Thus, nutritional deficiency has been modeled in rodents by examining prenatal protein deprivation, which produces PPI deficits in offspring (Palmer et al., 2004). Maternal vitamin D deficiency also results in brain and behavioral abnormalities related to schizophrenia (reviewed in Burne et al., 2004a; Burne et al., 2004b; Burne et al., 2006; Eyles et al., 2013; Eyles et al., 2009; Kesby et al., 2006; Schoenrock and Tarantino, 2016) with some evidence of PPI deficits associated with vitamin D deficiency in rodents (Burne et al., 2004b; Kesby et al., 2006). Additionally, obstetric complications such as pre-eclampsia, cesarian section, and perinatal hypoxia have been well documented and linked to schizophrenia in several independent studies (Cannon et al., 2002; Hultman et al., 1997; Zornberg et al., 2000), and modeled in animals (reviewed in Boksa, 2004; Meyer and Feldon, 2009a; Powell, 2010).

There is an increased appreciation for the role of psychological stress, both prenatal and early and childhood, in the pathogenesis of schizophrenia (reviewed in Koenig, 2006; Koenig et al., 2002). The effects of prenatal stress on schizophrenia-related behaviors in animals have been mixed and depend on the methods of inducing "stress" in the pregnant dam (Koenig, 2006; Koenig et al., 2005; Lee et al., 2007; Lehmann et al., 2000). Childhood trauma or negative childhood experiences contribute to the development of neuropsychiatric disorders (Read and Bentall, 2012). The evidence for an association between psychosocial stress and psychosis is mixed with some studies showing an association between adverse life events and psychosis (Johns et al., 2004; Miller et al., 2001; Shevlin et al., 2008; Wiles et al., 2006), and other studies failing to see an association between adverse lifetime events and psychosis in high risk individuals (Cannon et al., 2016; Mason et al., 2004), or higher rates

of childhood trauma in schizophrenia patients compared to controls (Kilian et al., 2017). Nevertheless, early postnatal stress has been assessed for its effects on schizophrenia-related behaviors with studies of more severe maternal deprivation (e.g. 24 hours) producing significant (Ellenbroek and Cools, 2000; Ellenbroek et al., 1998) or only mild or negligible deficits in PPI (Choy et al., 2009; Choy and van den Buuse, 2008), and shorter periods of maternal separation (e.g. 1–4 h/day) producing mild effects (Klug and van den Buuse, 2012) or no effect on PPI in rats (Finamore and Port, 2000; Weiss et al., 2001) or mice (Millstein et al., 2006). Many stress models, such as chronic unpredictable stress, social defeat stress, restraint stress, do not appear to affect PPI on their own. However, many of these manipulations have been used in combination with genetic risk factors (section 4.1) or other environmental manipulations (section 4.2) to affect PPI.

3.3 Adolescent Risk factors: social isolation and drugs of abuse

The juvenile/adolescent period is the time in which complex social behaviors develop and a critical period for remodeling of neural circuits important for social, emotional, and cognitive development (Casey et al., 2008; Giedd, 2008; Leon-Carrion et al., 2004). In schizophrenia, social withdrawal occurs early in the course of illness, prior to symptoms of psychosis, and predicts conversion to psychosis (Addington et al., 2008; Cannon et al., 2008; Moller and Husby, 2000). We have argued that social isolation and withdrawal in the course of schizophrenia can both *trigger* chronic stress cascades and be a *consequence* of the functional impairment resulting from premorbid social cognitive deficits in mental illness (Powell and Swerdlow, 2015). Because of the profound impact of social isolation and withdrawal on psychiatric health and the importance of the juvenile/adolescent period in social interaction and social development, post-weaning social isolation has been studied extensively in rodents. We refer the reader to our recent, more extensive review on the topic (Powell and Swerdlow, 2015).

Several studies have shown that drug abuse in adolescence increases the risk of developing schizophrenia (Nielsen et al., 2017), particularly adolescent cannabis use (Andréasson et al., 1987; Arseneault et al., 2002; van Os et al., 2002). Epidemiological findings suggest a link between cannabis use and psychosis (Gage et al., 2016; Vaucher et al., 2017) and that use of cannabis leads to an onset of psychosis at an earlier age than those who develop psychosis without a history of cannabis use (Barnes et al., 2006; Donoghue et al., 2014). However, the role of cannabis in schizophrenia risk is still unclear, and likely involves an increased susceptibility in genetically or environmentally susceptible individuals (Caspi et al., 2005; Di Forti et al., 2012; van Os et al., 2002). The effects of cannabis use on PPI are mixed (see Discussion for more detail).

4. “Two Hit” Models of Risk factors of Schizophrenia

As reviewed above, early developmental factors are implicated in the pathogenesis of schizophrenia (Davis et al., 2016), and recent GWAS have identified multiple common schizophrenia risk alleles contributing small effect to disease risk (Owen et al., 2016). In addition to common variants with small effects, there is also evidence for the involvement of several large CNVs in schizophrenia (Ross et al., 2006). Additionally, there are several non-

genetic second-hits (substance abuse (McKetin et al., 2013), adolescent cannabis exposure (Moore et al., 2007), childhood abuse (Mortensen et al., 1999), and residential status (e.g. urbanicity; (Kelly et al., 2010) that act at different periods of neurodevelopmental stages to increase risk. Such factors might have relatively weak effects on their own but when acting at specific developmental stages in genetically susceptible individuals (Gene × Environment; G × E) or in individuals exposed to other environmental risk factors (Environment × Environment; E × E), these factor may lead to the development of schizophrenia. Evaluating causation of risk factors in human studies is difficult since the risk factors cannot be manipulated. One of the primary issues that is difficult to disentangle in human studies is whether risk factors are causal to disease or whether some other factor (or covariate) influences both the risk factor and disease (Kendler and Gardner, 2010).

During recent years much research has focused on “two hit” developmental animal models to fully understand the changes in brain anatomy and behavior present in schizophrenia. The timing of these hits during neurodevelopment is very important because they can cause differing outcomes, where early developmental hits can lead to more widespread abnormalities and later, or second hits, can cause more specific changes (Davis et al., 2016; Pantelis et al., 2003). Thus, many rodent studies have employed a “two hit” approach to test the hypothesis that maldevelopment during two critical time periods, e.g. early brain development and then adolescence, may lead to schizophrenia (Keshavan and Hogarty, 1999). Here we review recent research modeling combined genetic and environmental risk factors (G × E interactions) or combined environmental risk factors (E × E interactions) in preclinical studies with an emphasis on sensorimotor gating effects in the models.

4.1 Modeling Gene × Environment risk factors relevant to schizophrenia

Interaction between genetic risk factors and environmental stressors at specific developmental stages increases the chance of developing schizophrenia (Uher, 2014). Although the notion that schizophrenia results from a genetic predisposition followed by an environmental “hit” has been hypothesized for a number of years, only recently have these GxE interactions been evaluated in clinical studies (van Winkel et al., 2008). In human studies, GxE interactions have been reported for several candidate genes (Uher, 2014). One of the first examples showing an association between psychosis and a gene-environment combination was for the functional Val158Met polymorphism in catechol-*O*-methyltransferase (COMT). Specifically, individuals with the Val allele (i.e. the more efficient allele) that had used cannabis in adolescence had an increased risk for psychosis (Caspi et al., 2005); however, this initial study was not replicated in subsequent studies (De Sousa et al., 2013; Kantrowitz et al., 2009; Zammit et al., 2011; Zammit et al., 2007). Additionally, childhood maltreatment may interact with cannabis exposure and COMT to increase psychosis risk. Indeed, there have been two reports of an association between COMT genotype, childhood maltreatment, and cannabis (Alemany et al., 2014; Vinkers et al., 2013). Another gene-environment interaction was reported for the AKT1 gene and cannabis, with individuals carrying a polymorphism in AKT1 more likely to develop psychosis after cannabis use (Di Forti et al., 2012; van Winkel, 2011). Childhood maltreatment has been shown to interact with several genes to increase risk of psychosis, including BDNF (Alemany et al., 2011; although see Ramsay et al., 2013), FKBP5, a co-

chaperone of the glucocorticoid receptor (Collip et al., 2013), and SLC6A4, encoding the serotonin transporter, (Aas et al., 2012). *In utero* infections have also been evaluated in the context of gene-environment interactions and psychosis risk. For example, GRIN2B, a component of NMDA glutamate receptors, interacted with exposure to herpes simplex virus-2 *in utero* (Demontis et al., 2011), and preliminary evidence from systematic gene-environment interaction studies indicated that CTNNA3, which encodes a cadherin-associated protein, interacted with *in utero* cytomegalovirus exposure in schizophrenia cases (Borglum et al., 2014). Thus, there is increasing evidence for gene-environment interactions in schizophrenia risk. Whether or not these gene-environment interactions are relevant to sensorimotor gating in humans has yet to be determined. Nevertheless, some of these gene-environment interactions have been studied in animal models and here we summarize how GxE interactions have affected PPI in animal studies (Table 1).

4.1.1. Disrupted-in-schizophrenia 1 (DISC1)—Disrupted-in-schizophrenia 1 (DISC1) was one of the first genes implicated in the pathophysiology of schizophrenia based on studies in a large Scottish family. The mutation involves a balanced chromosome translocation on chromosome 1q42 (Blackwood et al., 2001; Millar et al., 2000). DISC1 is a synaptic protein involved in cell proliferation, differentiation, and migration (Brandon and Sawa, 2011; Jaaro-Peled et al., 2009). Several different lines of transgenic mice containing DISC 1 gene mutations have been created to investigate its role in behavior and brain development (Ji et al., 2014). Here we summarize the current studies investigating DISC1 mutant mice combined with environmental risk factors.

DISC1 × maternal immune activation: Lipina and colleagues created two point mutation mouse lines *DISC1*-L100P and *DISC1*-Q31L and showed that the schizophrenia related phenotypic effects were more pronounced in *DISC1*-L100P mice (Lipina et al., 2012; Lipina et al., 2011). Combining this point mutation with maternal immune activation by administration of a sub-threshold dose of PolyI:C (2.5 mg/kg) at GD 9 led to more robust PPI deficits and decreased startle amplitude in *DISC1*-L100P offspring compared to wildtype control mice. When MIA was combined with the *DISC1*-Q31L mutation, both *DISC1*-Q31L and PolyI:C (5 mg/kg) produced PPI deficits at 16 weeks, but these deficits were not further potentiated by their combination. Following the gestational exposure of PolyI:C, increased levels of interleukin-6 (IL-6) were more pronounced in *DISC1*-L100P compared to *DISC1*-Q31L mice or wild type controls. When an IL-6 antagonist was co-administered at the time of maternal immune activation, PPI deficits were rescued in *DISC1*-L100P mice (Lipina et al., 2013).

DISC1 × neonatal immune activation: Ibi and colleagues utilized transgenic dominant-negative mutant DISC1 to study genetic and environmental risk factors by injecting poly I:C (5mg/kg) between PND 2 & 6. Neither DISC1 mutation nor neonatal poly I:C administration produced any changes in PPI (Ibi et al., 2010).

DISC1 × prenatal lead exposure: Recently, prenatal lead exposure has been associated with an increased susceptibility of schizophrenia in adulthood (Opler et al., 2004). Lead (Pb^{++}) is a potent antagonist of NMDA receptors and it is possible that Pb^{++} contributes to

schizophrenia in genetically vulnerable individuals. Hence, another study examined the interaction of inducible mutant human *DISC1* (mh*DISC1*) with prenatal exposure to lead. Female, but not male, mhDISC1 mice with prenatal lead exposure showed mild PPI impairments (at low prepulse intensities 74 and 78dB) (Abazyan et al., 2014).

DISC1 × social defeat stress: Interactions between DISC1 point mutations and chronic social defeat have also been examined in *DISC1*-L100P and Q31L mice. Mutant *DISC1*-L100P mice showed lower PPI than WT mice and *DISC1*- Q31L mice. Chronic social defeat stress did not affect PPI in WT, *DISC1*-L100P, or Q31L mice. Thus, there was no evidence of significant gene × environment interactions for social defeat stress and *DISC1* mutations on PPI (Haque et al., 2012).

4.1.2. Nuclear receptor related 1 protein—The nuclear receptor related 1 (Nurr1) protein is a member of the orphan steroid hormone receptor family. Nurr 1 is expressed in mesencephalic dopaminergic neurons and is critical for their survival and differentiation (Kadkhodaei et al., 2009; Rojas et al., 2007). Nurr1 heterozygous mice showed reduced dopamine in both the mesolimbic and mesocortical dopamine pathways, suggesting that Nurr1 is involved in the maintenance of dopamine neurotransmission (Eells et al., 2002).

Nurr1 × maternal immune activation: To investigate the interaction of maternal immune activation and Nurr1, Nurr1 mutant (heterozygous deletion of the Nurr1 gene) mice were exposed to PolyI:C on GD 9. When tested in adulthood (PND 75-120), the combination of Nurr1 mutation and PolyI:C resulted in additive effects on PPI, with both genotype and gestational exposure exerting main effects and Nurr1 (+/−) mice exposed to PolyI:C showing the most pronounced PPI deficits (Vuillermot et al., 2012).

Nurr1 × social isolation: Another study investigated the interaction between Nurr1 and early postnatal social isolation. In this study, WT and Nurr1 null heterozygous mice subjected to social isolation from weaning were tested for PPI alterations after 12 weeks of isolation. Nurr1 heterozygous miceshowed decreased PPI after social isolation, with normal PPI associated with isolation rearing or genotype alone (Eells et al., 2006). Thus, social isolation potentiated the effects of Nurr1 mutation on PPI.

Nurr1 × infection: In a recent study, Nurr 1 (+/−) mice were infected with *Toxoplasma gondi* and tested in a behavioral battery of tests relevant to schizophrenia. Nurr 1 (+/−) mice showed reduced startle magnitude but no differences in PPI compared to WT controls before the infection. There were no gene × environment interactions in startle magnitude or PPI in male or female mice when tested 6 weeks after the infection (Eells et al., 2015).

4.1.3. Neuregulin 1—Another susceptibility gene studied for its association to schizophrenia and sensorimotor gating is Neuregulin 1 (NRG1). Indeed, a schizophrenia-related NRG1 polymorphism has been associated with prepulse inhibition in human controls (Roussos et al., 2011) and schizophrenia patients (Greenwood et al., 2011). NRG1 is involved in neuronal migration, synaptogenesis, and neuron-glial interactions in the developing brain, as well as excitatory and inhibitory neurotransmission in the adult brain

(Harrison and Law, 2006). Because of the role in schizophrenia and brain development, NRG1 is an intriguing target to examine gene-environment interactions.

NRG1 × cannabinoid administration: The effects of cannabinoids in NRG1 mutant mice have been examined in several studies with some limited evidence of differential sensitivity to the behavioral effects of tetrahydrocannabinol (THC). In one study THC increased PPI and reduced startle in NRG1 HET mice, but not in WT mice (Boucher et al., 2007). Chronic adolescent exposure to THC (10 mg/kg; 21 days) had no effect in either NRG1 HET or WT mice (Long et al., 2013). In a subsequent study, Boucher and colleagues (Boucher et al., 2011) investigated the interaction of NRG1 and cannabinoid administration during adulthood. Single administration of the synthetic cannabinoid CP55,940 decreased PPI in WT mice and increased PPI in NRG1 HET mice. On the other hand, CP55,940 decreased acoustic startle in both WT and NRG1 HET mice. Thus, there is limited evidence for an interaction between NRG1 and cannabinoids on PPI and startle, but the data do not suggest that NRG1 and cannabinoids have an additive or synergistic effect on reducing PPI; if anything, cannabinoids produced increases in PPI.

NRG1 × maternal immune activation: Another study explored the effects of maternal immune activation in heterozygous NRG1 TM-domain mice. PolyI:C- or saline-exposed offspring were further subjected to cross fostering. Although there was an overall effect of decreased PPI in NRG1 HET mice, no clear interaction between NRG1 genotype and PolyI:C treatment was observed. There was some evidence of a potentiation of the PPI deficit in NRG1 HET with PolyI:C exposure, but this interaction was not consistent and interacted in a complicated way with cross-fostering (O'Leary et al., 2014).

4.1.4. Other susceptibility genes

Reelin × hypoxia: Reelin glycoprotein is involved in synaptic plasticity and brain development. Reductions in Reelin mRNA and protein levels have been found in prefrontal cortex, hippocampus, and cerebellum of schizophrenia patients (Cassidy et al., 2010a; Cassidy et al., 2010b). To investigate gene-environment interactions Reeler mice (haploinsufficient for Reelin) were exposed to prenatal hypoxia (9% oxygen) on GD17 for 2 hours. PPI was assessed at 3 months of age in mice exposed to hypoxia (9% oxygen) and normoxia *in utero*. PPI was increased in both WT and Reeler mice prenatally exposed to hypoxia. Interestingly, startle amplitude was decreased in WT hypoxia mice and Reeler normoxia mice compared to control WT normoxia mice (Howell and Pillai, 2016). Thus, the combination of Reelin haploinsufficiency and hypoxia did not produce PPI deficits.

Reelin × corticosterone: To model HPA increases during chronic stress, male and female heterozygous Reeler mice received chronic corticosterone treatment in the drinking water for 21 days starting at 6 weeks of age. Corticosterone treatment reduced PPI in male WT mice but had no effect on PPI in male reeler mice, suggesting a potential protective effect of reelin deficiency (Schroeder et al., 2015).

PACAP × social isolation: Pituitary adenylate cyclase-activating peptide (PACAP) is a member of the vasoactive intestinal peptide (VIP)/secretin/glucagon superfamily and is

distributed widely in both brain and periphery (Waschek, 2013). Mice lacking Adcyap1 gene encoding PACAP (−/−) display several schizophrenia-related behavioral phenotypes that can be reversed by antipsychotics (Hashimoto et al., 2009; Hashimoto et al., 2001; Hashimoto et al., 2007; Tanaka et al., 2006). Four week old PACAP-null mutant and WT mice were housed in social isolation for two weeks. PACAP KO group-reared mice showed decreased PPI compared to WT group-reared mice. Social isolation also disrupted PPI in WT mice. PACAP KO mice reared in social isolation showed profound decrease in PPI compared to WT group-reared mice, indicating a significant G × E interaction in this model (Ishihama et al., 2010).

SNAP25 × prenatal stress: Synaptosomal-associated protein-25 (SNAP25) is a SNARE protein known to play a role in neurotransmitter release (Chen and Scheller, 2001) and long-term potentiation (Jurado et al., 2013). GWAS have indicated the involvement of the SNAP-25 genomic region in schizophrenia (Lewis et al., 2003). Additionally, altered levels of SNAP-25 were found in frontal cortex (Honer et al., 2002) and hippocampus (Davidsson et al., 1999) of patients with schizophrenia. Based on this genetic association, Jeans et al. conducted a GxE study utilizing *blind-drunk* (*Bdr*) mice that express defective SNAP25 protein due to a single amino acid substitution (167T) that disrupts the normal recycling of synaptic vesicles (Jeans et al., 2007). In this study *Bdr* mice were exposed to repeated prenatal variable stress carried out from GD 11.5 to 17.5. Male offspring were assessed in a battery of behavioral tasks at the age of 8–11 weeks. *Brd* mutants showed a significant PPI deficit compared to WT controls. *Brd* mutants exposed to prenatal stress showed enhancement of PPI deficits compared to non-stressed *Brd* mutants and prenatally stressed controls. These deficits were ameliorated by administration of clozapine in *Brd* mutants from both the stressed and non-stressed groups (Oliver and Davies, 2009), suggesting some degree of predictive validity in the model.

BDNF deficiency × adolescent drug abuse: Brain-derived neurotropic factor (BDNF) is growth factor involved in brain development and neuroplasticity, and altered BDNF signaling is reported in schizophrenia (Autry and Monteggia, 2012). Thus, a recent study evaluated the effects of repeated synthetic cannabinoid CP55,940 exposure for 3 weeks starting at PND42 in BDNF deficient mice. BDNF HET mice showed decreased PPI compared to WT mice, and repeated administration of CP55,940 did not alter PPI in WT females or males. Acute challenge with CP55,940 increased PPI, particularly in the “double hit” group (BDNF HET male mice exposed to chronic CP55,940) but these effects should be interpreted with caution since acute CP55,940 reduced startle magnitude, which could confound PPI results (Klug and van den Buuse, 2013). Thus, chronic CP55,940 did not produce the expected potentiation of PPI deficits in BDNF HET mice. Chronic adolescent methamphetamine administration was also examined for its effects in BDNF HET mice. While both male and female BDNF HETs showed decreased PPI, chronic METH during adolescence did not potentiate these PPI deficits or have an effect on its own (Manning and van den Buuse, 2013).

Tap 1 knock out × neonatal influenza A virus: Another study that looked at G × E interaction infected immunodeficient Tap 1 mice (due to targeted disruption of the gene

encoding MHC class 1 and therefore lack functional CD8+ T cells) with influenza virus during the neonatal period (PND 3&4). Virus-infected Tap 1 KO mice, but not WT control mice, had impaired PPI, indicating long-term deficits in sensorimotor gating in immune deficient mice exposed to neonatal infection (Asp et al., 2010).

GCPII × folate deficiency: Glutamate carboxypeptidase II is a neuropeptidase that is present in astrocytes and catalyzes N-acetylaspartylglutamate (NAAG) into glutamate and N-acetylaspartate (Berger et al., 1999; Luthi-Carter et al., 1998). GCPII is also involved in dietry folate metabolism and absorption (Devlin et al., 2000), and thus the combined effect of dietry folic acid deficiency and mutation of GCPII was examined in mice. On PND25 GCPII (heterozygous mice) were either assigned to control folate diet (2 mg/kg) or folate deficient diet (0.3 mg/kg folate). The combination of GCPII mutation and folic acid deficiency did not affect PPI (Schaevitz et al., 2012).

NMDA receptor × social isolation: Jiang et al, 2013 examined G × E interaction by postnatal deletion of NMDA receptor in subset of cortical interneurons combined with post-weaning social isolation in mice (Jiang et al., 2013). In this study Ppp1r2-Cre/floxed-GluN1 (NR1 KO) mice were generated that have 40–50% deletion of NR1 in inhibitory interneurons by PND21. NR1 KO mice showed impaired PPI compared to WT controls. Isolation rearing alone did not produce PPI deficits; however, PPI was impaired in NR1 KO mice reared in social isolation. Chronic treatment with apocynin (starting at the age of 2 weeks) prevented PPI deficits in NR1 KO group-reared and isolation-reared mice (Jiang et al., 2013).

4.2 Environment × Environment interactions

Many environmental risk factors have been implicated in schizophrenia such as malnutrition, prenatal exposure to infections, stress during neonatal and postnatal development, and substance abuse (reviewed in Section 3). There is evidence of additive effects of urbanicity, cannabis use, and childhood trauma on risk of psychotic experiences (Guloksuz et al., 2015) or between cannabis use and childhood trauma (Harley et al., 2010; Houston et al., 2008; Houston et al., 2011; Konings et al., 2012; Murphy et al., 2013). This section focuses on the role of two environmental “hits”, or environment-environment interactions, in rodent models of PPI.

4.2.1. Immune dysregulation or Infections—It is well established that *in utero* or maternal exposure to infection is associated with increased risk of schizophrenia in offspring (Brown and Susser, 2002). The emergence of schizophrenia pathology in infected offspring during adulthood depends on the timing of infection during gestational period (Buka et al., 2008; Cheslack-Postava et al., 2015). Of course, all individuals who are exposed to infections *in utero* do not go on to develop schizophrenia, thus consideration of genetic susceptibility and/or additional environmental insults are important. Animal models of maternal infection include gestational exposure to either the TLR 3 agonist polyinosinic-polyctidylic acid (poly I:C), a synthetic analogue of double-stranded RNA, or lipopolysaccharide (LPS), a bacterial endotoxin that activates TLR 4.

Maternal immune activation × stress: Several recent studies have evaluated the interaction of maternal immune activation and juvenile/adolescent stress in mice. Giovanoli et al. (2016) exposed pregnant dams to a subthreshold dose of PolyI:C (1 mg/kg) or saline on GD 9 and offspring were subsequently exposed to varied unpredictable stress between postnatal day 30 and 40 (i.e. Electric foot shock, restraint stress, swimming stress, food deprivation, repeated home cage changes applied to alternate days). Neither prenatal immune activation nor stress alone affected PPI; however, peripubertal unpredictable stress was associated with disruption of PPI in offspring born from Poly I:C-infected mice but not saline controls. Thus, the combination of maternal immune activation and peripubertal stress disrupted PPI. Preventive treatment with minocycline (tetracycline antibiotic) before and throughout the exposure of stress prevented the PPI deficits in stressed PolyI:C offspring (Giovanoli et al., 2016).

An earlier study investigated the combined effects of maternal immune activation on GD 12 (20mg/kg) and juvenile stress in C57BL/6 mice. Pups born form poly I:C-infected dams were subjected to restraint stress for 3 consecutive days from PND 33 to 35. Juvenile restraint stress or gestational Poly I:C alone did not alter PPI when tested 24 hours after the last stress episode on PND 36; however, mice exposed to both maternal immune activation and juvenile restraint stress did show PPI deficits (Deslauriers et al., 2013). Administration of the antioxidant α-lipoic acid before restraint stress prevented the PPI deficits in the two-hit group and reduced oxidative stress levels in frontal cortex (Deslauriers et al., 2014). Other studies have failed to show a potentiating effect of stress on maternal immune activation-induced PPI deficits in rats (Yee et al., 2011), suggesting potential species differences in the interaction. Nevertheless, the prevention of some of the behavioral effects of the combined maternal immune activation and juvenile/pubertal stress with drugs targeting inflammation or oxidative stress indicates that this combined model may be useful in drug development.

4.2.2. Social isolation—As reviewed above, social isolation in rodents is a developmental manipulation in which rodents are raised singly-housed in absence of any social interaction with other rats or mice. In this section we summarize the effects of combining social isolation with other developmental insults on PPI.

Neonatal domoic acid × social isolation: A recent study investigated the interaction between neonatal domoic acid injections and isolation rearing in Sprague-Dawley rats. Domoic acid is an AMPA/kainite agonist that, when administered during the second postnatal week, results in later onset of behavioral phenotypes consistent with schizophrenia (Burt et al., 2008a, b). In this dual-hit study, pups were injected with domoic acid (20 μg/kg *s.c.*) from postnatal day 8–14 and then assigned to group-housing or social isolation at weaning. Isolated rats showed PPI deficits. Interestingly, domoic acid treatment increased PPI in isolates but no effects were found in group housed animals (Marriott et al., 2016).

Social isolation × methamphetamine: Another study examined E × E interaction by utilizing social isolation from weaning and chronic methamphetamine administration. Female Wistar rats were reared in social isolation or group housing from weaning. Another environmental hit was added by administering escalating doses of methamphetamine (2–6 mg/kg b.i.d) for 16 days from PND 35 to 50. On PND 78, female rats were tested in PPI.

Social isolation alone reduced PPI in rats, and chronic administration of methamphetamine reduced PPI to the same extent in isolation-reared and group-housed controls (Strauss et al., 2014).

Neonatal NMDA antagonist × Social isolation: Lim and colleagues examined E × E interaction by combining perinatal MK801 treatment with social isolation in Sprague-Dawley rats. Rats were injected with MK801 (0.2 mg/kg) from PND 7 to 10 and either isolated or group housed at the time of weaning (PND 21). When tested in adulthood (PND 91) rats exposed to MK-801 and social isolation showed robust PPI deficits (Lim et al., 2012). Similarly, Gaskin et al evaluated the effects of two developmental insults by combining neonatal phencyclidine (PCP) injections and social isolation from weaning in Lister-hooded rats. Rats that received both insults showed deficits in PPI, which were not present in groups subjected to social isolation or neonatal PCP administration alone (Gaskin et al., 2014). These studies indicate that neonatal NMDA antagonist administration, combined with post-weaning social isolation, produce robust disruptions in PPI.

4.2.3. Maternal Separation

Maternal separation × Conditioned avoidance × PCP: Another study utilized a multiple hit approach during different developmental stages in Sprague- Dawley rats to examine combined environmental insults (Chen et al., 2011). Rats were subjected to maternal separation from PND 3 to 10 (first-hit) and then to avoidance conditioning on PND 49–56 (second-hit) and injected with PCP (3 mg/kg) immediately after each avoidance training (third-hit). The three hits were then assessed for their effect on change in %PPI from adolescence to adulthood. Maternal separation blocked the adolescent to adult increase in PPI observed in saline-treated rats but this effect was not evident in rats exposed to avoidance training, suggesting that the second hit remediated some of the effects of the first hit. This study demonstrates the complexity of using multiple “hits” within the same experiment, when triple interactions are being tested.

Maternal separation × corticosterone treatment: In this study Wistar rats underwent maternal deprivation on PND 9 for 24 h and then corticosterone treatment for 2 weeks in young adulthood (starting at 8 weeks of age). There was no effect of maternal separation, chronic corticosterone, or their combination on baseline PPI. Apomorphine disrupted PPI in all groups except those sustaining the combination of maternal separation and chronic corticosterone; whereas, amphetamine disrupted PPI in all groups except the maternally deprived groups. Thus, rather than an increased sensitivity, rats exposed to maternal deprivation and early adult corticosterone showed a decreased sensitivity to dopamine agonists (Choy and van den Buuse, 2008).

5. Discussion

Here we summarize schizophrenia risk factors, neurodevelopmental animal models, and the current findings from two hit models of these risk factors published in recent years. As reviewed above, we focused on PPI because of its strong relationship with schizophrenia, its heritability, and its sensitivity to developmental risk factors. Taken together, the studies

suggest that some gene and environment combinations result in more pronounced PPI deficits than either manipulation alone. For example, post-weaning social isolation potentiates the PPI deficits in inhibitory neuron-specific NR1 KO mice (Jiang et al., 2013), PACAP KO mice (Ishihama et al 2010), and Nurr1 HET mice (Eells et al., 2006), and prenatal stress potentiates PPI effects in SNAP25 (Brd) mutants (Oliver and Davies, 2009). Inflammation is another second hit that has been shown to enhance PPI deficits in genetic mutants. Neonatal influenza produced PPI deficits in immunodeficient Tap 1 KO mice (Asp et al., 2010), and maternal immune activation with PolyI:C increases PPI deficits in Nurr1 HET mice (Vuillermot et al., 2012) and DISC1 mutant mice (Lipina et al., 2013) but failed to interact with NRG1 HETs (O'Leary et al., 2014). The evidence for adolescent cannabinoids interacting with genetic risk factors is less compelling. There was no evidence that THC or the synthetic cannabinoid agonist CP55,940 potentiated the effects of genetic risk factors on PPI (Long et al., 2013). In fact, where there was an interaction with genotype, cannabinoids actually *increased* PPI in the mutant mice (Boucher et al., 2007; Boucher et al., 2011; Klug and van den Buuse, 2013). Considering that the effects of cannabis use on PPI are mixed in the clinical literature, these results may not be surprising. In adults, chronic marijuana use was not associated with PPI (Quednow et al., 2004); however, adult marijuana users that initiated use during adolescence had decreased PPI compared to non-using controls in a task that involved attending to the auditory stimuli (Kedzior and Martin-Iverson, 2006, 2007; Scholes and Martin-Iverson, 2009). The timing of marijuana initiation may be important to the effects on PPI. In fact, there is evidence that cannabis use *increased* PPI in "at risk" and "early psychosis" subjects (Cadenhead, 2011). Human studies indicate that age of cannabis use onset, duration of use, and stage of illness at the time of PPI testing contribute to the effects of cannabis use on PPI. Thus, recapitulating these effects in animal models may be particularly challenging, and it is not clear the direction of prediction (i.e. increased or decreased PPI) considering the equivocal effects of cannabis use on PPI in humans. Animal studies of cannabinoids and PPI are equally equivocal. Acute and repeated juvenile and peri-pubertal administration of the cannabinoid agonist, WIN55,212-2, disrupted PPI in adulthood (Schneider et al., 2005; Schneider and Koch, 2002, 2003; Wegener and Koch, 2009); however, other groups have failed to replicate these findings (Bortolato et al., 2005; Bortolato et al., 2014). Adolescent exposure to other drugs of abuse, including amphetamine and alcohol, do not appear to affect PPI in adulthood (Coleman Jr et al., 2011; Richetto et al., 2013). Thus, there is not a lot of compelling evidence from animal studies that exposure to drugs of abuse in adolescence has an enduring effect on PPI. It should be noted, however, that animal studies use either THC or synthetic cannabinoid agonists; whereas, humans smoke cannabis, which contains many constituents in addition to THC, making it difficult to model drug exposure in model organisms. These clinical and preclinical studies of cannabis and PPI suggest that PPI may not be the most relevant measure of the link between cannabis use and psychosis.

Regarding double hits of two environmental/developmental risk factors, there is evidence for the combined effects of maternal immune activation and adolescent stress on PPI in mice (Deslauriers et al., 2013; Giovanoli et al., 2013), but not in rats (Yee et al., 2011). Additionally, perinatal NMDA antagonism combined with post-weaning social isolation produced deficits in PPI in rats (Gaskin et al., 2014; Lim et al., 2012). Many of these

psychosocial stressors and neonatal/prenatal immune activation manipulations, as well as risk gene models, often have effects on their own, making it difficult to determine additivity or synergy in the combined models or producing ceiling effects in which further disruption is not achievable. For example, although both social isolation and adolescent methamphetamine reduced PPI in rats, the combination had no additive or synergistic effect (Strauss et al., 2014). Similarly, prenatal hypoxia produced PPI deficits in Het and KO Reeler mice (Howell and Pillai, 2016). To address the issue of main effects and to provide adequate behavioral windows to assess potentiation, many studies have used sub-threshold manipulations (e.g. lower, sub-threshold dose of PolyI:C as used in Giovanoli et al., 2013) and/or heterozygous mutant mice to assess effects of double hits. This approach may provide models that better mimic the nature of genetic and environmental interactions in the human population.

Most of the G × E models we reviewed looked at one susceptibility gene and environmental factors; however, schizophrenia involves more than one gene (Owen et al., 2016) and thus studies will likely also begin examining multiple risk genes to investigate epistatic interactions. Additionally, most of the studies reviewed focused on the neuronal function of susceptibility genes; however, the function of these genes in other cells such as glia should also be considered. For example, DISC1 is expressed in astrocytes and microglia (Seshadri et al., 2010). Mutant DISC1 expressed in astrocytes decreased production of D-serine in astrocytes, which was associated with a greater response to MK-801 in PPI (Ma et al., 2013). Similarly, astrocytes also produce BDNF (Girardet et al., 2013; Sun et al., 2014) and overexpression of BDNF in hippocampal astrocytes produces anxiolytic and antidepressant-like effects (Quesseveur et al., 2013); however, behavioral changes relevant to schizophrenia have not been evaluated. It will be interesting to look at the role of these susceptibility genes or multiple developmental insults in microglia and/or astrocytes in GxE or ExE interactions.

One observation emerging from these studies is sex-specific effects of G × E and E × E interactions. In schizophrenia, sex-specific effects are observed in the course and symptoms of the illness with males having an earlier onset than females, thus it is not surprising that animal models related to the disease report different effects in males and females. Additionally, schizophrenia is increasingly considered a neurodevelopmental disorder (Section 3.0) and the developmental timing of environmental insults can greatly impact the pattern of results in the model. For example, maternal immune activation by administration of Poly I:C at early and late gestation affect behavior of the offspring differently (Meyer et al., 2006; Smith et al., 2007). Similarly, the effects of postnatal hypoxia on PPI depend on the timing and severity of the hypoxia. For example, hypoxia at PND 9 had no effect on PPI even though it altered mesolimbic dopamine neurochemistry (Sandager-Nielsen et al., 2004). Sub-chronic exposure to hypoxia from PND 4–8 did produce PPI deficits in adult rats (Fendt et al., 2008). Similarly, when a multiple-hit approach is applied, more attention should be paid to the timing of environmental insult and first and second order interactions among these hits, either gene or environment.

Animal models of schizophrenia utilizing multiple hits should have face (behavioral similarities, symptoms homology), construct (replicates pathology), and predictive (show pharmacological reversal of deficits or lack of pharmacological response) validity. Many of

the models reviewed here have met these criteria and have shown that combining genetic and environmental risk factors or multiple developmental/environmental risk factors improves the model. Whether or not these models will offer better predictive validity for drug development is not yet known. The appeal of genetic and/or developmental models is the opportunity to intervene early in the progression of pathology and test potential preventive treatments. In several “single hit” models, particularly prenatal exposure to PolyI:C and neonatal ventral hippocampal lesion, preventative treatments have shown the ability to block some of the behavioral abnormalities, including reduced PPI (reviewed in Millan et al., 2016). In mice exposed to gestational PolyI:C, typical and atypical antipsychotics as well as antidepressants prevent PPI deficits in the model (Meyer et al., 2010). In the neonatal ventral hippocampal lesion model, the emergence of PPI deficits was prevented by adolescent treatment with antioxidants (Cabungcal et al., 2014). Perinatal NMDA antagonist (phencyclidine administration, PND 7–11)- induced PPI deficits were prevented by the mGlu5 positive allosteric modulator AD47273 and the nicotinic alpha-7 partial agonist, SSR180711 (Kjaerby et al., 2013). Preventive treatments have also been tested in a few two-hit models as well. In an effort to target the neuropathology in the model, pubertal treatment with minocycline prevented PPI deficits in mice exposed to MIA+juvenile stress (Giovanoli et al. 2016). In another study in inhibitory neuron-specific NR1 KO mice exposed to social isolation, chronic treatment with apocynin reversed PPI deficits in the mice (Jiang et al., 2013). Of course, none of these novel therapies have been shown to fully reverse the neuroanatomical and neurochemical deficits in individuals suffering from schizophrenia, but there is increasing evidence that neuroinflammation and oxidative stress may affect a subset of patients with schizophrenia and thus demonstrating efficacy in double hit models adds to our understanding of these putative risk factors and potential treatment approaches.

Another important point to consider in assessing models of risk factors for neuropsychiatric disease is that most of these risk factors, including both genetic and environmental, increase risk only moderately. For example, the estimated odds ratio for the exposure to obstetric complications increasing the risk of schizophrenia is 2.0, indicating a rather low relative risk associated with obstetric complications (Rapoport et al., 2005). Thus, it is not surprising that manipulating these risk factors on their own, or even in combination with one additional risk factor, does not produce profound behavioral alterations in model organisms. We must also realize that most environmental risk factors for schizophrenia are complex and occur in the context of other risk factors and/or protective factors, making them difficult to translate to animal models. For example, adolescents that smoke cannabis and are also socially isolated from peers may be more at risk than adolescents who smoke cannabis and have a supportive social network. Maternal infection combined with inadequate prenatal care may put the offspring more at risk than maternal infection combined with good prenatal care. The goal of animal models should not be to recapitulate the messy complexity and variability of the human condition, however. After all, the goal of animal research is to create simplified models to systematically manipulate variables of interest and control for as many other extraneous variables as possible. The hope is that these models will move beyond mere characterizations of behavioral/cognitive constructs deficient across neuropsychiatric disorders toward models with predictive power for drug development (Powell et al. 2012). Perhaps the combination of susceptibility genes and developmental risk factors will provide

better models for medication development for neuropsychiatry. As our knowledge of the clinical condition improves, our models should attempt to more closely represent etiological risk factors and/or neuropathology in order to develop more predictive models for drug development (Moore, 2010). Combining risk factors, as reviewed here, moves the field toward developing these more refined models with potential for better translatability. We are well aware that all aspects of a heterogeneous disease will not be recreated in model organisms with a genetic mutation and/or developmental risk factors. Additionally, no single phenotype such as PPI is either necessary or sufficient to substantiate a model as having relevance to neuropsychiatric disease. Thus, as human studies materialize with more neurobiologically defined functional domains (as outlined in initiatives such as the NIH RDoC), translating these measures or "endophenotypes" to animal models will improve. As a preclinical behavioral measure, PPI has shown predictive validity in rodent pharmacological models, cross species homology, and sensitivity to genetic and neurodevelopmental risk factors for schizophrenia. Whether or not PPI has fulfilled its promise of informing clinical neuropsychiatry has been recently considered (Swerdlow et al., 2016; Swerdlow and Light, 2016). In terms of the double hit models reviewed here, PPI does not appear to be a sensitive measure of combined risk factors in many cases. Some double hit paradigms (e.g. MIA + adolescent stress), however, have shown synergistic effects on PPI that can be prevented by novel therapeutics, indicating a potentially enhanced ability to discover novel therapeutics (Giovanoli et al., 2016). While these rodent models are not without shortcomings, they are more closely approximating etiology by examining multiple risk factors. Hence, further consideration of environmental risk factors and systematic approaches to studying these combined risk factors would greatly benefit the genetic models. As the primary "hits" from GWAS studies emerge, future studies should focus on a sub-set of genes and either combine these candidate genes to examine epistatic interactions or, as reviewed here, combine candidate genes with environmental/ developmental risk factors.

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Table 1

Summary of selected models of Gene × Environment interactions on sensorimotor gating

Susceptibility Gene	Model description/background/rationale	Second Hit	Effects on PPI	Prevention/Treatment strategies	References
	DISC1				
DN-DISC1(dominant-negative DISC1 under the expression control of CaMKII promoter (DN-DISC1; line 10)	DISC1 plays important role in brain development	PolyI:C 5 mg/kg or saline (PND2-6)	Ø PPI & Ø PA in WT vs TG, PolyI:C/WT vs		Ibi et al. 2010
DISC1-L100P	Missense mutation in exon 2 of DISC1 at L100P in mice	Prenatal PolyI:C (2.5 mg/kg) on GD 9	Ø PPI in poly I:C vs Sal, ↓PPI in DISC1-L100P & DISC1-L100P/ Poly I:C vs WT & L100P/Sal	Co-administration of IL-6 antagonist PPI deficits in DISC1-L100P/poly I:C mice	Lipina et al 2013.
DISC1-Q31L		Prenatal PolyI:C (5 mg/kg) on GD	16wks: ↓PPI in poly I:C vs Sal, ↓PPI in DISC1-Q31L vs WT. No potentiatio n of PPI deficit in DISC1-Q31L/Poly I:C		Lipina et al 2013
DISC1 (Transgenic model of inducible expression of dominant negative human hDISC1 in forebrain)		Prenatal exposure to Pb++	Ø PPI in Pb^{++} vs Reg ↓PPI in F hDISC1/Pb^{++} vs hDISC1/Reg mice.	Administration of D-serine, reversed PPI hDISC1/Pb^{++} in F	Abazyan et al. 2014
DISC1 DISC1 (L10P and Q31L mutants)		Chronic social defeat stress	Ø PPI in WT/NS vs WT/CSD & $Q31L^{+/-}$/NS vs $Q31L^{+/-}$/CSD; ↓PPI in $L100P^{+/-}$/NS vs WT/NS; No GxE		Haque et al,2012
	Nurr1				
Nurr1 (Heterozygous constitutive deletion of Nurr1)	Nurr1 plays important role in differentiation, migration and survival of DA ergic neurons	Prenatal PolyI:C (5mg/kg) on GD9	↓PPI in Nurr1 +/− vs WT. ↓PPI in WT/poly I:C vs WT/Veh; ↓PPI in Nurr1 +/−/PolyI:C mice		Vuillermot et al., 2012
Nurr1 (Nurr1-null mice by homologous recombination at exon 3)		Social Isolation	Ø PPI in WT/Iso vs WT/Soc. ↑PPI in Nurr1+/−/Soc vs WT/ Soc. ↓PPI in Nurr1+/−/Iso vs WT/Iso and WT/Soc.		Eells et al 2006
Nurr1		Infection with Toxoplasma gondi	↓Baseline startle & Ø PPI in Nurr1+/− vs WT in M&F. Ø PPI after infection		Eells et al 2015
	Neuregulin				
NRG1 TM HET (HET NRG1 transmembrane domain	NRG1 may represent a SZ susceptibility gene. Involved in neuronal migration, synaptogenesis, neuronglia interactions.	Acute and subchronic administratio n of CP55,940 (0.4mg/kg)	↓PPI in NRG1 HET/Veh vs WT/ Veh. ↓PPI in WT/CP at 74dB. ↑PPI in HET/CP vsWT/CP		Boucher et al 2011

Susceptibility Gene	Model description/background/rationale	Second Hit	Effects on PPI	Prevention/Treatment strategies	References
knock-out targeting exon 11)					
NRG1 TM HET		THC (5 & 10mg/kg)	Ø PPI in WT mice, THC ↑PPI in NRG1 +/− mice; ↓PA in NRG1 +/− at high dose (10 mg/kg)		Boucher et al 2007
NRG1 TM HET		Prenatal poly I:C on GD 9 (5mg/kg). Pups were crossfostered from PND 0–2	↓PPI in NRG1 +/−, NRG1 +/−/ PolyI:C & ↓PPI inNRG1+/−poly I:C infected dams and cross-fostered to poly I:C infected dams		O'Leary et al 2014
NRG1 TM HET		THC (10 mg/kg, IP) 21 days during adolescence (PND31–52)	Ø PPI after acute or chronic THC or following washout in WT or Het mice; Ø PPI in NRG1 Het		Long et al. 2013
	Reelin				
Reelin KO	Reelin levels in brains of SZ are reduced.	Prenatal Hypoxia	↓PPI by hypoxia in both WT and HET mice. No GxE interaction		Howell & Pillai 2016
Reelin HRM		CORT treatment	↓PPI in WT CORT vs WT CON in M not in F, Ø PPI in HRM CON vs WT CON & HRM/ CORT vs WT CORT		Schroeder et al. 2015
	PACAP				
PACAP KO, M	PACAP affects neurotransmission; potential SZ susceptibility gene	Social Isolation	↓PPI in KO vs. WT (PA data not shown); ↓PPI in WT/Iso vs WT/ Soc. ↓PPI KO/Iso vs WT/Iso.	EE: ↓PPI in KO & WT	Ishihama et al. 2010
	SNAP25				
SNAP25 (Blind drunk mutant)	Snap25 is a SNARE protein and is linked to SZ	Prenatal Stress	↓PPI in WT vs *Brd* mutants in NS, PNS ↓PPI in WT vs *Brd* mutants. ↓PPI in PNS *Brd* mutants than NS mutants. Significant GxE interaction	CLO: Reversed PPI in NS & PNS *Brd* mutants	Oliver and Davies, 2009
	BDNF				
BDNF	BDNF is involved in brain development and neuroplasticity and is implicated in pathophysiology of SZ	Chronic METH during late adolescence and early adulthood	↓PPI in HET M&F mice; Ø PPI in METH- treated mice; No GxE interaction on baseline PPI		Manning & van den Buuse, 2013
BDNF		CP (0.4mg/kg) during young adulthood	Ø Baseline PPI following G or E insult. ↓PPI in HET vs WT. ↑PPI in HET/CP vs HET/Sal M after acute CP challenge. ↑PPI in WT/Veh, WT/CP, HET/Veh and HET/CP after acute CP challenge.		Klug & van de Buuse 2013
	Tap1				

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Susceptibility Gene	Model description/background/rationale	Second Hit	Effects on PPI	Prevention/Treatment strategies	References
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.	Neonatal influenza	Influenza infection on PND 3 or 4: ↓PPI in adult KO mice (during ISI block), trend for ↑PA in infected mice in startle threshold block; Ø PPI & Ø PA in infected vs. non-infected WT C57 mice		Asp et al. 2010
	GCPII				
GCPII	GCPII Glutamate carboxypeptidase II catalyzes NAAG and is also involve in dietary folic acid metabolism	Dietary folic acid deficiency	Ø PPI in WT FD diet vs WT control diet & GCPII Het vs WT & GCPII Het/FD diet vs WT control diet.		Schaevitz et al., 2012
	NMDA Receptor				
NR1 (Ppp1r2-Cre/floxed-GluN1mice has GluN1 deletion in a subset of cortical interneurons)	NR1 NMDA receptor hypofunction is implicated in schizophrenia. NR1 knock out mice have early postnatal deletion of NMDA receptor from corticolimbic interneurons	Social isolation	↓PPI in NR1 KO vs WT, Ø PPI in WT/SI vs WT/Soc. ↓PPI in NR1KO/SI & NR1 KO/Soc vs WT/Soc	Chronic apocynin (from postnatal week 2) prevented ↓PPI in NR1/Soc and NR1/SI	Jiang et al. 2013

Abbreviations: BDNF brain derived neurotropic factor, Brd blind drunk mutant, CaMKII Ca^{2+}/calmodulin-dependent protein kinase II, CLO clozapine,CORT corticosterone, CP CP55,940, CSD chronic social defeat, dB decibel, DISC-1 Disrupted-In-Schizophrenia-1, DIZ dizocilpine, DN dominant-negative, EE environmental enrichment, F female, FD folate deficient, G gene, GCPII Glutamate carboxypeptidase II, GD gestational day, HRM heterozygous reelin mice, IL interleukin, ISI interstimulus interval, KO knockout, M male, METH metamphetamine, NAAG N-acetylalpha L-aspartyl-L-glutamate, NR1 NMDA receptor subunit, NRG neuregulin, ns not significant(ly), NS non stressed, Nurr1 nuclear receptor, PA magnitude of response to pulse alone, PACAP pituitary adenylate-cyclase-activating polypeptide, Pb^{++} lead, PND postnatal day, PNS prenatal stress, PolyI:C polyinosinic: polycytidylic acid, PP prepulse, PPI prepulse inhibition of startle, Reg regular diet, Sal saline, SCID Severe combined immunodeficiency, SI social isolation, SNAP-25 synaptosomal-associated protein of 25kDa, SNP single nucleotide polymorphism, SZ schizophrenia, TG transgenic, THC tetrahydrocannabinol, TM transmembrane domaine, WT wild-type, ↓ decreased, ↑ increased, Ø unchanged, −/− homozygous mice, +/− heterozygous mice

Table 2

Summary of selected animal models of Environment × Environment interactions on sensorimotor gating

First hit	Model description/background/rationale	Second Hit	Effects on PPI	Prevention/Treatment strategies	References
	Prenatal/Maternal Immune activation				
Prenatal PolyI:C (1 mg/kg) GD 9	In utero or maternal exposure with synthetic double stranded RNA PolyI:C or bacterial endotoxin LPS	Varied unpredictable stress between PND30–40 in C57BL/6	Ø PPI in poly I:C vs Veh or Stressed vs NS. ↓PPI in polyI:C/Stressed vs polyI:C/NS. Significant ExE interaction	MIN (30mg/kg) before and during duration of unpredictable stress attenuated ↓PPI in ExE group.	Giovanoli et al, 2016
Prenatal PolyI:C (20 mg/kg) GD 12		Juvenile restraint stress from PND33–35 in C57BL/6	Ø PPI in poly I:C or Stressed vs controls. ↓PPI Poly I:C/stressed. Significant ExE interaction	α-LA before each stress episode reversed ↓PPI in poly I:C/stressed mice	Deslauriers et al, 2013; Deslauriers et al 2014
Prenatal PolyI:C (4 mg/kg) GD 15		Juvenile varied stress from PND27–29 in Sprague Dawley rats	↓PPI in poly I:C vs Sal. Ø PPI in stressed rats vs NS. Ø PPI in poly I:C/ stressed vs Sal/NS. No ExE interaction		Yee et al, 2011
LPS (5μg/kg) on GD15/16		Iron deficiency from GD2–PND7	Ø PPI in LPS vs Sal. ↓PPI in ID/Sal vs IS/Sal and ID/LPS vs IS/Sal. No ExE interaction		Harvey et al, 2014
	Post-weaning social isolation				
Social isolation from PND21 in Wistar rats	Rodents raised singly housed in absence of any social interaction with other rats or mice immediately from weaning.	Escalating METH (0.2–6 mg/kg) on PND35–50	↓PPI in Iso vs Soc, ↓PPI in Iso/METH, Soc/METH Vs Soc/Veh. No ExE interaction		Strauss et al, 2014
Social isolation in Wistar rats on PND25		Peripubertal administration of poly I:C (20 mg/kg) for 5 days from PND38–48	↓PPI in Iso/Sal vs Soc/Sal, Iso/poly I:C vs Soc/Sal on PND60. ↓PPI Iso/Sal vs Soc/Sal, Soc/poly I:C vs Soc/Sal & Iso/poly I:C vs Soc/Sal on PND80. Significant ExE interaction.		Lukasz et al, 2013
	Neonatal NMDA antagonist/Neurotoxin				
Neonatal MK-801 (0.2 mg/kg) from PND7–10 in Sprague Dawley rats	Neonatal NMDA antagonist exposure to model hypothesized NMDA hypofunction in schizophrenia and as a general neonatal insult	Social isolation from PND21	↓PPI in Iso vs Soc on PND77&91. ↓PPI in MK-801/Iso vs Soc/Veh on all intensities at PND91.	CLO injection before PPI on PND84 attenuate ↓PPI in MK801/isolates vs social/veh	Lim et al, 2012
Neonatal PCP (10mg/kg) on PND7,9,11 in Lister-hooded rats		Social isolation from PND23	Ø PPI in Iso vs Soc, PCP/Soc vs PCP/ Veh. ↓PPI in PCP/Iso vs Veh/Soc. Significant ExE interaction		Gaskin et al, 2014
Neonatal DOM injections from PND8-14 in Sprague-Dawley rats	Domoic acid (DOM) is a kainite agonist which produces neurotoxicity	Social isolation from PND21 for 12 weeks	↓PPI in Iso vs Soc. ↑PPI in Iso/DOM vs Iso/Sal. No ExE interaction		Marriott et al, 2016
	Maternal separation				

First hit	Model description/background/rationale	Second Hit	Effects on PPI	Prevention/Treatment strategies	References
Maternal separation from PND 3–10 in Sprague-Dawley rats	Rodents deprived perinatally from stimulations from dam and littermates.	Avoidance conditioning (PND49–56) and immediately injected with PCP after every conditioning session	Ø PPI in MS vs Non-MS. Effects of PCP and conditioned avoidance are not clearly documented		Chen et al 2011
Maternal separation on PND 9 for 24h in Wistar rats		Adolescent Corticosterone treatment at 8 weeks of age	Ø PPI in MS vs Non-MS. AMPH & APO ↓ PPI in Non-MS & Non-MS/CORT. APO ↓ PPI in MS. Ø PPI in MS by AMPH. Ø PPI by APO & AMPH in MS/CORT. DPAT ↓ PPI in Non-MS, Non-MS CORT, MS & MS/CORT		Choy et al 2008

Abbreviations: AMPH amphetamine, APO apomorphine, CLO clozapine, DOM domoic acid, DPAT 8-hydroxy-dipropylaminotetralin, E environment, EE environmental enrichment, F female, GD gestational day, ISI interstimulus interval, Iso isolate, IS iron sufficient, ID Iron deficient, LA lipoic acid, LPS lipopolysaccharide, M male, NS non-stressed, MIN minocycline, MS maternal separation, METH methamphetamine, NMDA N-Methyl-D-aspartate, PA magnitude of response to pulse alone, PCP phencyclidine, PND postnatal day, PNS prenatal stress, Poly I:C polyinosinic: polycytidylic acid, PP prepulse, PPI prepulse inhibition of startle, SI social isolation, Soc socials, SZ schizophrenia, Veh vehicle, ↓ decreased, ↑ increased, Ø unchanged