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Animal models of gene–environment interaction in schizophrenia: A dimensional perspective

Yavuz Ayhan [a,e], Ross McFarland [a,d], Mikhail V. Pletnikov [a,b,c,d,*]

[a] Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, USA
[b] Solomon H Snyder Department of Neuroscience, Johns Hopkins University School of Medicine, USA
[c] Department of Molecular and Comparative Pathobiology, Johns Hopkins University School of Medicine, USA
[d] Department of Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health, USA
[e] Hacettepe University Faculty of Medicine, Department of Psychiatry, Turkey

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ABSTRACT

Schizophrenia has long been considered as a disorder with multifactorial origins. Recent discoveries have advanced our understanding of the genetic architecture of the disease. However, even with the increase of identified risk variants, heritability estimates suggest an important contribution of non-genetic factors. Various environmental risk factors have been proposed to play a role in the etiopathogenesis of schizophrenia. These include season of birth, maternal infections, obstetric complications, adverse events at early childhood, and drug abuse. Despite the progress in identification of genetic and environmental risk factors, we still have a limited understanding of the mechanisms whereby gene–environment interactions (G × E) operate in schizophrenia and psychoses at large. In this review we provide a critical analysis of current animal models of G × E relevant to psychotic disorders and propose that dimensional perspective will advance our understanding of the complex mechanisms of these disorders.

Contents

Abbreviations: GEI, gene–environment interaction; DSM-V, the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders; GWAS, genome-wide-association studies; SNP, single nucleotide polymorphism; PGC, Psychiatric Genomics Consortium; MHC, the major histocompatibility complex; CNV, copy number variations; DISC1, Disrupted-In-Schizophrenia 1; LOD, logarithm of odds; MIA, maternal immune activation; HSV, herpes simplex virus; CMV, cytomegalovirus; HLA, the human leukocyte antigen; HERV, human endogenous retroviruses; *FOX2P*, the Forkhead box protein P2 gene; MRI, magnetic resonance imaging; METH, methamphetamine; ADHD, attention deficit hyperactivity disorder; TLR, toll-like receptor; DOX, doxycycline; GD, gestation day; mPFC, the medial prefrontal cortex; Nurr1, The nuclear receptor related 1 protein.

* Corresponding author at: Johns Hopkins School of Medicine, Department of Psychiatry and Behavioral Sciences, 600 North Wolfe Street, CMSC 8-117, Baltimore, MD 21287, USA.
E-mail address: mpletnik@jhmi.edu (M.V. Pletnikov).

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1. Introduction

Awareness of the burden of psychiatric disorders is growing, as is the body of research on the causes of mental illnesses. With 0.5% of the total human population affected by schizophrenia over their lifetime (Saha et al., 2005), it represents a major public health concern, having an overall disability burden exceeding that of many infectious diseases (Murray et al., 2012). Schizophrenia is a debilitating psychiatric disorder characterized by positive (e.g., hallucinations and delusion), negative (e.g., social withdrawal and flat affect) and cognitive impairments. These abnormalities usually lead to a lifetime disability for affected patients. The disease is commonly diagnosed in the early 20s, with the diagnosis being made on average 5 years earlier in males than females (Tandon et al., 2008).

The heterogeneous symptoms and clinical manifestations of schizophrenia overlap with those of other major mental illnesses (i.e., bipolar disorders). Prompted by the growing genetic evidence, the conceptual scope of the disorder has been questioned (Berrios et al., 2003), leading to the development of perspectives for psychotic disorders that are independent of diagnosis category, including dimensional approaches and the Research Domain Criteria (RDoC) matrix. In their influential review, van Os and Kapur (2009) propose that symptoms of psychotic disorders be grouped into five dimensions, including psychosis (“the positive-symptom dimension”), avolition and social withdrawal (“the negative-symptom dimension”), cognitive impairments (“the cognitive-symptom dimension”); and affective disorders clustered into depressive and manic symptoms. Another indication of the shifting diagnostic landscape within psychotic disorders can be seen in the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V). This latest edition now includes dimensional assessments, with the classification of domains being expanded over those described above, but based on the same principles (Heckers, 2013).

Concurrent with these changes, research in psychiatry has worked to identify genetic variants and environmental adversities that may be significant risk factors for schizophrenia. However, there is a growing consensus that the pathogenesis of the disorder may rely on a constellation of causative factors that lead to disease. Collectively, the interplay of these factors is referred to as gene–environment interaction or G × E (van Os and Kapur, 2009; Uher, 2014).

Recently, there have been published a number of reviews of human and animal studies of G × E in schizophrenia (Ayhan et al., 2009; van Winkel et al., 2010; Kannan et al., 2013; Réthelyi et al., 2013; Hida et al., 2013; Cash-Padgett and Jaaro-Peled, 2013; Karl, 2013). The novel feature of this review is to propose dimensional approach to animal models instead of recapitulating the entire disorder by adhering to the clinical diagnostic criteria. We argue that dimensional perspective will be more successful in addressing the molecular mechanisms underlying G × E in order to facilitate search for new therapeutic interventions of this complex disorder.

2. Genes and environment in schizophrenia

2.1. Genetic bases

The etiology of schizophrenia is poorly understood, and the disease defies any single definition of where risk may originate. A genetic component of risk is well established with twin studies showing an estimated heritability of schizophrenia in the range of 70–80% (Neale and Sklar, 2015). With regards to genetics of the disease, the greatest progress has come from the large sample-sized genome-wide-association studies (GWAS). The Psychiatric Genomics Consortium (PGC), established in 2007, includes more than 500 investigators from 25+ countries and deserves strong consideration in this field (Sullivan, 2010). The Consortium has been collecting genome wide single nucleotide polymorphism (SNP) data worldwide to establish meta-analyses that highlight common disease causing polymorphisms. The leading hypothesis resulting from this work is that the genetic architecture of schizophrenia is similar to that of height, Crohn’s disease or diabetes and relies on common variants of small effects (Sullivan et al., 2012).

The latest PGC paper describes the genotyping data of 36,989 cases and 113,075 controls (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). With this sample size, 108 loci of genome wide significance were identified, with 83 being newly described. More than 80% of these loci were found in or near known gene regions, including haplotypes with polymorphisms coding for dopaminergic receptors, glutamatergic transmission proteins and calcium gated voltage channels. When the causal sequences were mapped with epigenetic markers of specific tissues, the risk variants were found to be enriched in the brain, particularly in the cortex and the striatum, compared to other organs. This study identified genes that encode for the proteins involved in the pathophysiological mechanisms of schizophrenia, including dopaminergic and glutamatergic systems. In addition, this work reported single nucleotide polymorphisms on chromosome 6, where the major histocompatibility complex (MHC) genes are located. Although this region contains genetic elements beyond those involved in immunity, the MHC locus variants suggest etiological relevance of immune genes and inflammatory pathways (Anon, 1999; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). GWAS share concerns about the population stratification, clinical and genetic heterogeneity, the absence/presence of marginal effects, and the multiple testing problem as reviewed in (Price et al., 2010).

Another development in schizophrenia genetics is the demonstration of the role of structural variations (Walsh et al., 2008; Purcell et al., 2014). Some of these mutations are rare and have a

moderate-to-large effect. Most are related to copy number variations (CNVs) as well as other types of structural genomic variation including deletions, duplications, and chromosomal rearrangements with potentially different pathogenic mechanisms and phenotypic outcomes (Levinson et al., 2011; Merikangas et al., 2014; Ruderfer et al., 2013; Timms et al., 2013; Warnica et al., 2014). The rate of CNVs in schizophrenia patients is increased, with deletions being observed more frequently than duplications (Buizer-Voskamp et al., 2011; Szatkiewicz et al., 2014). Structural variations can be inherited or originate de novo, and their role appears limited to a small fraction of patients (Ruderfer et al., 2013). There have been reports on prevalence of de novo CNV mutations in genes encoding for synaptic proteins (Xu et al., 2008, 2012; Kirov et al., 2012). Notably, some de novo genetic variants found in patients with schizophrenia overlap with those found in autism spectrum disorder and intellectual disability (Fromer et al., 2014), suggesting the common genetic bases of these developmental brain disorders.

Several families were found to carry structural variations affecting single genes with large impacts (Goate et al., 1991; Rogaev et al., 1995; Klein and Westenberger, 2012). One well-known example is Disrupted-In-Schizophrenia 1 (*DISC1*) identified in the large Scottish pedigree carrying a balanced translocation t(1:11) (q43, q21) that segregates with schizophrenia, schizoaffective disorder, recurrent major depression, alcohol dependence and conduct disorder (St Clair et al., 1990). The LOD (logarithm of odds) score for this translocation was found to be 7.1 for all mental disorders and 3.6 for schizophrenia. The translocation is inherited with a dominant mode and reduced penetrance (Millar et al., 2000). Another example of a rare mutation in *DISC1* is a frame-shift mutation of *DISC1* that segregates with schizophrenia and schizoaffective disorder in a US family (Sachs et al., 2005). Although the pathogenic potential of this mutation remains to be clearly demonstrated (Green et al., 2006), the latest study has provided some interesting insights into the mechanisms whereby this mutation may contribute to abnormal neuronal development (Wen et al., 2014). For in-depth discussions of schizophrenia genetics, the readers are referred to several comprehensive reviews of the topic (McGrath et al., 2013; Mitchell and Porteous, 2011; Sullivan et al., 2012; Harrison, 2015).

Despite the progress in GWAS, the search for the genetic architecture of schizophrenia continues, since the identified variants explain only a small proportion of the overall phenotypic variance. Studies of the potential role of environmental stressors and their interplay with genetic liabilities are anticipated to better explain the etiology of schizophrenia (Réthelyi et al., 2013).

2.2. Environment

Many environmental adversities have been associated with schizophrenia, including in utero exposure to infection, perinatal complications, and stressful events during prenatal and early postnatal development, malnutrition, infection and substance abuse (Brown, 2011; Meyer and Feldon, 2010). It has been argued that at least some cases of schizophrenia might be directly related to strong effects of vitamin D deficiency during pregnancy (McGrath et al., 2010), childhood abuse (Mortensen et al., 1999), or adolescent cannabis exposure (Moore et al., 2007).

2.3. Epigenetic factors

There is an increasing appreciation that, in addition to DNA sequence and the environment, epigenetic alterations may contribute to psychiatric disorders. Indeed, epigenetic modification is a major mechanism whereby adverse effects of environmental risk factors impact gene expression (Egger et al., 2004; Feinberg, 2007; Bagot and Meaney, 2010). Here, we only briefly review the epigenetics of schizophrenia and refer readers to several recent reviews of the topic (Petronis et al., 1999; Labrie et al., 2012; Abdolmaleky et al., 2005).

Epigenetic mechanisms are predominantly related to chemical modifications of the genome that influence gene expression without changing the DNA sequence (Martin et al., 2011; Helin and Dhanak, 2013). Although DNA methylation and histone modifications comprise the major processes of epigenetic modifications, a growing variety of noncoding RNAs are also being increasingly recognized as another important epigenetic mechanism regulating gene transcription (Hannon, 2002; Chitwood and Timmermans, 2010; Dethoff et al., 2012). Similar to the early days of psychiatric genetics, most recent epigenetic studies have evaluated epigenetic abnormalities in so-called candidate genes, focusing on genes involved in synaptic neurotransmission, oxidative stress, inflammatory pathways or myelination (Svrakic et al., 2013; Pishva et al., 2014; Shorter and Miller, 2015). These studies are being followed by methylome-wide association analysis (MWAS) in patients with psychotic disorders. MWAS finds DNA methylation differences in numerous genetic loci related to neurotransmitter systems and neurodevelopment. Thus, epigenetic studies have convincingly demonstrated that altered epigenetic processes may mediate environmental effects to increase the risk for schizophrenia and other psychotic disorders (Petronis et al., 1999; Labrie et al., 2012; Ibi and González-Maeso, 2015).

Furthermore, growing evidence indicates that complex interactions between genetic variants, environmental factors and epigenetic modifications likely moderate genetic liability toward psychotic disorders. This review then focuses on the role that gene–environment interactions (G × E) play in the pathogenesis and pathophysiology of schizophrenia (van Os, 2009; Uher, 2014).

3. Gene–environment interplay

Gene–environment interdependence encompasses several scenarios of how genes and environment work together in a particular disorder (Kendler and Eaves, 1986; Rutter et al., 2006). As indicated above, a frequent example of gene–environment interdependence includes environmentally triggered epigenetic modifications (Labrie et al., 2012; Akbarian, 2014). De novo mutations have been also associated with advanced paternal age (Matheson et al., 2011; Goriely et al., 2013). Additive effects of genetic and environmental factors describe what is commonly thought of when liability genes and adverse environment act together to increase one's chances to develop a disease. In their influential early review, Kendler and Eaves indicate two central features of this interaction: "the effects of exposure to a given environment on liability to illness are the same regardless of a phenotype; and the probability of an individual's exposure to a given environment is independent of the individual's genotype" (1986). As separate from interaction, gene–environment correlations then refer to genetic control of exposure to the environment (Kendler and Eaves, 1986; Dick, 2011). In other words, exposure to environment is driven by individual predisposition to choose a particular milieu. There are three main types of these correlations. Passive correlation denotes effects of environment stemmed from a genetic predisposition external to the subject. For example, a genetically controlled parental behavior can influence early life environment that, in turn, shapes a child's personality and behavior. Active correlations and evocative correlations are believed to result from the genes of an individual and are related to actively selecting a preferred environment, or stimulating the existing environment to respond to the individual (Kendler and Eaves, 1986; Dick, 2011). Gene–environment interaction (G × E) includes a genetic control of responses to protective or adverse environmental factors, and

dependency of genetic effects on an environment. Such that genetic effects can have a stronger impact in one environment in comparison to another (Kendler and Eaves, 1986; Rutter, 2008; Rutter et al., 2006; Moffitt et al., 2005; Rutter et al., 2006; Dick, 2011).

Human G × E studies have emphasized the importance of integrating identified genetic risks with environmental factors also associated with disease (van Winkel et al., 2010). The following sections summarize the main findings in recent human and animal studies of G × E in schizophrenia.

3.1. Immune dysregulation and microbial pathogens

3.1.1. Human studies

In utero or maternal exposure to influenza, *Toxoplasma gondii* and infections of reproductive organs are identified risk factors for schizophrenia in offspring (Canetta and Brown, 2012; Brown, 2011).

Thus far, only a handful studies have explored G × E in the cases of infection exposure.

One study investigated simplex and multiplex families and found that odds of exposure to cytomegalovirus (CMV) were increased in multiplex families and significant linkage with the D6S2672 region in CMV positive patients (Kim et al., 2007). A study from the same group with a larger sample size and a more detailed genetic evaluation found a positive association between seropositivity for HSV-1 or CMV and a SNP, rs1051788, located to the MHC region (Shirts et al., 2007). The same polymorphism was associated with greater reduction of volume in the prefrontal cortex of schizophrenia patients (Prasad et al., 2010). When focusing on the immune signaling, SNPs located within the *IL18R1* gene or *IL18RAP* gene were all found to be associated with HSV-2, CMV and HSV-1 seropositivity in schizophrenia patients (Shirts et al., 2008). A recent study evaluating the possible interaction between genetic background and exposure to infection in schizophrenia patients utilized a GWA approach in 4500 European cases and controls (Borglum et al., 2014). Neonatal blood samples obtained from Danish filter papers were analyzed for CMV serology in a subgroup of 488 patients and controls. A significant interaction was observed between CMV exposure and a SNP (rs7902091) in the catenin-alpha 3 gene *CTNNA3*, which was not associated with schizophrenia without exposure. Another study evaluated the association of HSV-2 seropositivity with several different polymorphisms from the GRIN family of genes. The GRIN family encode for different NMDA receptor subunits (NLM, 2014). The authors report an interaction between maternal HSV-2 seropositivity and the *GRIN2B* genetic variations, rs1805539 and rs1806205 (Demontis et al., 2011).

Several studies have reported associations between schizophrenia and season of birth, which may be considered a proxy for maternal infection risk (Torrey et al., 1997; Mortensen et al., 1999). One Japanese study (Narita et al., 2000) found an association between incidence of winter births and the human leukocyte antigen (HLA)-DR1 in patients with schizophrenia. In contrast, Tochigi et al. report no association between HLA-A24 or HLA-A26 and season of birth in schizophrenia (2002). Chotai and colleagues investigated associations between psychosis and polymorphisms within the genes for the tryptophan hydroxylase, serotonin transporter and dopamine D4 receptors. They found that the effects of the polymorphisms were dependent on season of birth (2003). No association with winter birth was reported for the SNP (rs1801133) in the methylenetetrahydrofolate gene in a case–control study (Muntjewerff et al., 2011).

Another group of risk factors that might be influenced by the season of birth are those related to nutritional status during pregnancy. Among maternal nutritional alterations, reduced vitamin D (Sullivan et al., 2013), folate levels (Glaser et al., 2010) and elevated homocysteine levels (Brown et al., 2007) were associated with increased risk of schizophrenia in the offspring. Vitamin D deficiency is not only associated with prenatal malnutrition, but also observed in adult schizophrenia patients (Bao et al., 2012; Belvederi Murri et al., 2013). Maternal or child genetic background may be important during the process. For example, methylene tetra-hydro-folate reductase (*MTHFR*) gene C677T polymorphism influences DNA methylation, therefore it may have effect on regulation of schizophrenia-associated genes. In particular, TT genotype, in the presence of low folate levels, decreases DNA methylation (Friso et al., 2002). In different studies, more schizophrenia subjects were found to carry TT genotype than controls (Gilbody et al., 2007; Lewis et al., 2005), and this effect may be more prominent in Asians (Hu et al., 2014).

In addition to maternal immune activation, another possible mechanism whereby microbial infection can interact with risk factors is related to the possibility that some risk factors (e.g., DISC1) may be used by microbes for replication and dissemination (Carter, 2009). Certain features of retroviral genetic interference could also provide a mechanistic explanation for how microbes may interact with genetic liability. Human endogenous retroviruses (HERV) are integrated in the human genome as a result of retroviral infection in germ line cells at several points during our evolution. They can be transmitted person to person, and are thought to play a role in the diversity of the human genome (Leboyer et al., 2013). A specific type of HERV, called HERV-W, has been associated with schizophrenia in several studies (Karlsson et al., 2001, 2004; Huang et al., 2006; Weis et al., 2007; Yao et al., 2008; Dickerson et al., 2012) but negative findings have been also reported (Frank et al., 2005). Notably, HSV-1 and influenza have been demonstrated to activate HERV-W elements, suggesting that environmentally precipitated re-activation of HERV-W may be an important intermediary factor by which exogenous infections contribute to the disorder (Leboyer et al., 2013; Young et al., 2013).

3.1.2. Animal studies

One of the most popular approaches to model maternal infection in animal preparations is to stimulate pregnant females with compounds that target toll-like receptors (TLRs), leading to activation of the innate immune response (Meyer and Feldon, 2010, 2012). Prenatal treatment with either the TLR3 agonist polyinosinic–polycytidylic acid (poly (I:C)), an analog of double-stranded RNA, or the TLR4 agonist, Gram-negative lipopolysaccharide (LPS), produces brain and behavior changes that resemble aspects of neurodevelopmental disorders such as schizophrenia and autism (Meyer, 2014). Although basic research has suggested that maternal immune activation (MIA) following exposure to infection may play an important role in causing brain and behavioral pathology analogous to that found in patients with schizophrenia, the exact mechanisms of how microbes can bring about abnormal neurodevelopment remain poorly understood. Further, most animal models that use prenatal immune activation as an environmental factor typically utilize high doses of immune activating compounds, beyond what would be physiologically present during natural infection. This strategy allows the criticism that these models often misrepresent the effect of infection and also the validity of the claim that prenatal infections are responsible for disease. Our group and others have recently proposed that, given the clear genetic components related to schizophrenia risk, experimental studies should focus on studying interactions between prenatal infection and susceptibility genes. Integrating G × E modeling in this system would allow the advance of our understanding of MIA as it relates to the pathogenesis of schizophrenia (Kannan et al., 2013; Brown, 2011). Many animal models of G × E have used this approach with mice carrying variants of candidate genes.

3.1.2.1. DISC1 models. The first models to use prenatal immune activation in G × E studies were the ones with expression of variants of Disrupted-In-Schizophrenia (*DISC1*) (Millar et al., 2000). *DISC1* has been implicated in various brain functions, including neural proliferation, migration, dendritic arborization and spine formation and the maintenance of synapses (Brandon and Sawa, 2011; Wen et al., 2014). Recently, it has been also demonstrated that *DISC1* is involved in mitochondrial functions, oligodendrocyte differentiation and astrocyte functioning (Eykelenboom et al., 2012; Kim et al., 2012; Ma et al., 2013; Park et al., 2010; Wood et al., 2009). Different *DISC1* mouse models have been generated. For detailed information on those models, interested readers are referred to previously published reviews (Ayhan et al., 2011b; Jaaro-Peled, 2009).

Our group generated a transgenic model for inducible expression of mutant human DISC1, a putative product of the translocation (Pletnikov et al., 2008a). In this Tet-off model, one can regulate expression of mutant DISC1 in a cell-specific manner with administration of doxycycline (DOX). Expression of mutant DISC1 in forebrain neurons leads to increased spontaneous locomotor activity, decreased social interaction and increased aggressive behavior in males and decreased spatial recognition memory in Morris water maze in females. These behavioral changes are accompanied by lateral ventricles enlargement and reduced dendritic arborization (Pletnikov et al., 2008b). We also found that prenatal expression of mutant DISC1 was sufficient to produce smaller brain size and aggression in mice. Prenatal expression also resulted in lateral ventricle enlargement and associated increased sensitivity to psychostimulants in male mice and depressive-like behaviors in female mice (Ayhan et al., 2011a).

In order to assess possible effects of G × E in mutant DISC1 mice, we exposed them to prenatal immune stimulation using poly I:C treatment (Abazyan et al., 2010). Pregnant mice carrying both mutant DISC1 and control fetuses were injected with 5 mg/kg poly I:C or saline (as a control group) at gestational day (GD) 9. It was found that mutant DISC1 altered the normal pattern of poly I:C-induced secretion of cytokines in the fetal brains. In adulthood, prenatal poly I:C exposure increased anxiety-like and depressive-like behaviors and decreased sociability only in mutants but not in controls. Poly I:C also altered functioning of the hypothalamus–pituitary–adrenal (HPA) axis by blunting the corticosterone response to restraint stress in mutant mice. The morphometric measurements showed that poly I:C decreased the volumes of the amygdala and periaqueductal gray matter, the areas involved in the brain circuitries of fear- and anxiety related responses in rodents (Canteras et al., 2010). We also demonstrated that expression of mutant DISC1 was necessary during the entire period of prenatal and postnatal development required for the immune challenge to produce the observed neurobehavioral alterations (Abazyan et al., 2010). One of the main outcomes of this study is that pre-existing phenotypic alterations in mutant DISC1 mice were not significantly affected by MIA. Instead, we observed that mutant mice challenged with MIA began to demonstrate the neurobehavioral changes resembling affective disorders. This outcome is consistent with the genetic data that *DISC1* can be associated with different psychiatric diseases and also underscores importance of testing different behavioral abnormalities that may not be congruent with a specific diagnostic category but rather reflect different dimensions of the psychopathological continuum as discussed later.

Another group used a mouse model of constitutive expression of mutant *DISC1* and evaluated the effects of poly I:C applied during early postnatal development (Hikida et al., 2007; Ibi et al., 2009). Neonatal mutant and control mice were injected with poly I:C for 5 days from postnatal day 2 to 6 and the effects were evaluated at adulthood. Early postnatal poly I:C exposure impaired a short-term memory assessed in Y maze and worsened novel object recognition in both control and mutant mice. When compared to control saline-treated mice, mutant *DISC1* mice treated with poly I:C had impaired fear memory, increased locomotor activity, decreased social interaction and increased aggressive behaviors. The decreased number of parvalbumin positive cells in medial prefrontal cortex (mPFC) and the increased number of BrdU positive cells, an indicator of neurogenesis, in the granular cell layer of the dentate gyrus of the hippocampus were found only in mutant *DISC1* mice treated with poly I:C. This study demonstrated how an environmental factor can exacerbate pre-existing mild schizophrenia resembling abnormalities (e.g., reduced parvalbumin reactivity) in DISC1 mice (Ibi et al., 2010).

Synergistic effects of genetic variants and environmental challenge were also described by the study that used *DISC1* mutant lines, with exon 2 missense point mutations resulting in Q31L and L100P amino acid changes (Clapcote et al., 2007). In the initial paper, 31L mutant mice demonstrated increased immobility in the forced swim test (FST), decreased sociability and decreased sucrose consumption, consistent with a depressive-like phenotype. L100P mutant mice had increased locomotor activity, decreased PPI and Latent Inhibition and a poor memory assessed in T maze. Antidepressant treatment improved FST in Q31L mutants whereas antipsychotics, rolipram (an inhibitor of PDE4 that binds to DISC1 (Millar et al., 2005)) and a GSK3 inhibitor (VP1.15), increased PPI in L100P and Q31L mice (Lipina et al., 2013). Decreased neurogenesis, the number of neurons in the cortex, and altered neuronal morphology were observed in both mutant models, suggesting cortical maldevelopment (Lee et al., 2011).

Q31L and L100P heterozygous animals were challenged with MIA induced by poly I:C at GD9. MIA reduced sociability, worsened pre-existing impairment in PPI, and affected novel object recognition in L100P mutants that were considered a model of schizophrenia-related abnormalities (Clapcote et al., 2007). Prenatal immune challenge up-regulated expression of IL-6 in the fetal brains, with the strongest effect being found in L100P mice. Notably, anti-IL6 treatment reversed the effects of poly I:C on PPI and LI in mutant mice, supporting the previous findings that IL-6 may play a leading role in mediating adverse effects of maternal immune activation (Smith et al., 2007; Lipina et al., 2013).

3.1.2.2. Nurr 1. The nuclear receptor related 1 protein (NURR1) is an inducible transcription factor, an orphan member of the steroid/thyroid nuclear receptor superfamily. *Nurr1* expression starts early during development and continues throughout adulthood. *Nurr1* is expressed in mesencephalic dopamine neurons and is responsible for their differentiation (Buervenich et al., 2000; Moore et al., 2008; Xing et al., 2006). Given the role of dopamine neurotransmission in the pathophysiology of schizophrenia, the function of this protein was evaluated in *Nurr1* knockout (KO) mice. The heterozygous *Nurr1* KO mice displayed increased activity at baseline and after administration of PCP or amphetamine. Both basal and drug-induced hyperactivity was reversed by haloperidol (Rojas et al., 2007). In cognitive tests, no learning deficit was observed but memory retention was significantly impaired in males in passive avoidance test. In addition, increased immobility on the second day of FST was found, suggesting a depression-like response in mutant mice. The alterations in the dopamine and serotonin metabolism were detected in the frontal cortex, striatum and hippocampus of mutant animals (Rojas et al., 2007). It should be noted that some of these results were not replicated in a recent study (Moore et al., 2008).

Urs Meyers group evaluated the effects of G × E in *Nurr1* mutant mice exposed to MIA with poly I:C at GD17. When tested at

postnatal days (PND) 70–120, synergism of the effects of both factors was observed in increased locomotor activity, startle reactivity, PPI and latent inhibition (LI). Immunohistochemical analysis revealed decreased tyrosine hydroxylase staining in the nucleus accumbens (NAc) and PFC and increased COMT staining. Interestingly, poly I:C increased production of IL-6, IL-10 and TNF-α only in control but not mutant mice, which had already decreased levels compared to wild-type littermates (Vuillermot et al., 2011, 2012).

The study of O'Leary and colleagues (2014) is an example of using a sophisticated design of cross-fostering in an attempt to distinguish multiple effects of G × E and control for dams' behaviors following an adverse environmental exposure during pregnancy. The authors examined the neurobehavioral schizophrenia-related interactions between prenatal immune activation with Poly I:C and disruption of the schizophrenia risk gene, Neuregulin 1 (*NRG1*). A variety of schizophrenia-related behavioral abnormalities were found depending on the combinations of *Nrg1* disruption, prenatal insult and cross-fostering. The authors argue that multiple time-dependent interactions that involve individual genes interacting with diverse biological and psychosocial environmental factors should be taken into account and recapitulated in animal models.

In a recent exciting paper, *Nurr1* KO mice were exposed to chronic infection with *T. gondii* and were tested in an emergence test, activity in an open field and with a novel object, response to bobcat urine and prepulse inhibition of the acoustic startle response (PPI) prior to and 6 weeks after infection. *T. gondii* infection produced a greater elevation of open field activity in *Nurr1* HET mice consistent, with the hypothesis that the *Nurr1* genotype can exacerbate parasite-induced behavioral abnormalities (Eells et al., 2015).

Another example of using live pathogen associated with schizophrenia is a series of studies performed by a Swedish group who infected neonatal immunodeficient (*Tap1* KO) mice lacking functional CD8 (+) T cells with influenza A/WSN/33 virus. Three to four months after the infection, deficits in working memory, increased rearing activity and anxiety were observed in KO but not WT mice. No group differences were found in virus replication, distribution or clearance. One possible mechanism for G × E in this model may be related to a more pronounced glia response in *Tap1* KO mice to viral infection (Asp et al., 2009). A subsequent study evaluated long-term effects of the infection on PPI and transcription of genes encoding enzymes in the kynurenine pathway and levels of kynurenic acid (KYNA) that have been shown by the same group to be activated in this viral model. Influenza infection up-regulated transcripts encoding indoleamine-pyrrole 2,3-dioxygenase (IDO), degrading tryptophan in the first step of the kynurenine pathway, and transiently increased KYNA in the brain of infected mice. At age 5–6 months, neonatally infected *Tap1* KO but not WT mice showed reduced PPI. The authors conclude that a neonatal infection targets the brain kynurenine pathway contributing to deficient sensorimotor gating in genetically vulnerable mice (Asp et al., 2010; Liu et al., 2014).

The main drawbacks of the G × E MIA models as reviewed include: (1) limited examinations of dose- and time-dependent effects of MIA; (2) a handful of molecular factors analyzed, calling for a global unbiased profiling with RNA-seq; (3) focus on "conventional" cytokines while practically leaving out measures of other immune factors, particularly peripheral markers of the immune response of dams and offspring. Although using poly I:C or LPS has helped to generate several exciting G × E models, their utility may be limited as these immune activators are artificial compounds and mimic only some aspects of MIA. More studies with live pathogens relevant to human conditions (e.g., *T. gondii*) are clearly needed. It would be also important to expand use of anti-inflammatory treatment in animal models to further explore the potential of this therapeutic approach.

3.2. Stressful factors

There is an increasing appreciation that stressful events during prenatal and early postnatal development are major environmental risk factors for psychiatric illness and that stress can disrupt brain functioning in a variety of ways (Fine et al., 2014; Dvir et al., 2013). Here, we overview the recent human and basic research on the role of stressful factors in schizophrenia.

3.2.1. Human studies

3.2.1.1. Residential status. Residential status, where a person was born, raised or still lives, has been considered an established risk factor for schizophrenia. Systematic reviews assessing the effects of residential status demonstrated that the majority of studies, both with register-based and interview-based methodologies, found a positive association between any period of urban living and schizophrenia (Kelly et al., 2010). A recent meta-analysis which pooled registry based data from over 22,000 cases collected in Denmark, Sweden and Netherlands demonstrated that with an increasing "urban exposure index", the incidence rate for schizophrenia increases. Urbanicity increases the odds risk of developing schizophrenia 2.4 times compared to rural residency (Vassos et al., 2012). The effect of urban residency was also evident for psychotic disorders at large and for "psychotic-like symptoms" in different studies from several different regions of the world (Kelly et al., 2010; Szoke et al., 2014; van Os et al., 2001). In addition, some studies reported positive association between urbanicity and development of other mental disorders, such as bipolar disorder (Paksarian et al., 2014), post-traumatic stress disorder (Reeves et al., 2013), depression and anxiety symptoms (Lundberg et al., 2009) but contradicting findings also exist (Baxter et al., 2006; Breslau et al., 2014).

Findings from NEMESIS (Netherlands Mental Health Survey and Incidence Study) pointed to the possible genetic interaction with urbanicity for the first time. Proband patients with a family history of psychosis have significantly higher risks to develop psychosis with increased urbanicity than probands without the same family history (van Os et al., 2003, 2004). The authors suggest that as many as 60–70% of individuals with familial liability who had also experienced urban exposure went on to develop a psychotic disorder. In the aforementioned studies, urbanicity was rated according to the degree of the density of the population in address counts per square-kilometer and the effect of prominent urbanicity was discussed as an environmental factor that interacts with genetic liability. This interaction resulted in an increase in risk for psychotic illness, rather than 'lower level of urbanicity' having a protective effect. The reader should note, however, that these studies, by design, provide correlative data and models are often needed to identify causal disease origins within the observed risk factors.

3.2.1.2. Childhood trauma. For the last two decades, epidemiological research has rekindled interest in the role of early childhood adversity in schizophrenia (Rossler et al., 2014). A Swedish national cohort study of more than 2 million subjects evaluated the hospital inpatient registry against childhood living circumstances, including parental status, housing status, socioeconomic level, and employment status. The authors found the increased number of adverse childhood events in hospitalized patients (Wicks et al., 2005). Frequency of episodes of childhood trauma was found to be higher in patients compared to healthy controls or their siblings. It was also reported that trauma increased the severity of schizophrenia symptoms, was then also associated with high scores of schizotypy in the siblings and even healthy subjects (Heins et al., 2011), enhanced severity of prodromal symptoms

(Thompson et al., 2009), or decreased cognitive competencies in patients with schizophrenia (Shannon et al., 2011). All these findings are consistent with the notion that childhood trauma can increase the risk for psychosis or moderate the severity of positive symptoms. Beyond the impact of childhood adverse events on adult psychopathology in schizophrenia, the same profile also exists in anxiety disorders, depression, substance use disorders, and bipolar disorder (Gilman et al., 2014; Green et al., 2010; Pietrek et al., 2013). In this context, one could describe the effects of childhood adversity as nonspecific.

Considering that childhood abuse is a strong environmental risk factor for the development of psychotic symptoms and disorders, there has been considerable interest in understanding its association with genetic risk. This association between abuse and disease could be due to genetic factors influencing exposure to traumatic environments or increasing sensitivity to the detrimental impact of abuse. However, one recent study exploring the interaction between early life abuse and genetic markers showed no significant additive effect of childhood abuse combined with the known risk haplotype of the nitric oxide synthase 1 adaptor protein (*NOSAP1*) gene (Husted et al., 2010). In another study, Alemany et al. (2011) evaluated interactions between childhood abuse and the *BDNF* Val66Met polymorphism on the prevalence of positive and negative symptoms in adult patients. This work showed that compared to Val homozygotes, Met carriers had higher scores on a psychotic experiences scale if childhood adversities were present, indicating interaction between childhood abuse and genetics.

McCarthy-Jones and colleagues examined potential G × E between SNPs of the Forkhead box protein P2 gene (*FOX2P*), which was previously weakly associated both with auditory verbal hallucination (AVHs), and childhood emotional abuse (Lai et al., 2001). Human *FOXP2* is known to have a role in the development of speech and language in humans (Lai et al., 2001). Data on parental child abuse and *FOXP2* SNPs previously linked to AVHs were evaluated in people with schizophrenia-spectrum disorders, both with (n = 211) and without (n = 122) a lifetime history of AVHs. The authors report that although SNP frequencies did not differ between abused and non-abused groups, there was a statistically significant interaction between childhood parental emotional abuse and rs1456031 in predicting lifetime experience of AVH. Curiously, this interaction was found to be specific to AVHs, and was not found for non-verbal auditory hallucinations. The findings are a preliminary but promising example of G × E in which a weak genetic effect can be moderated by childhood abuse (McCarthy-Jones et al., 2014).

Although not directly related to schizophrenia, Rabl et al. provide an example of an endophenotypic evaluation of additive gene–environment effects on the hippocampus, the volume changes in which have been linked to chronic stress. This MRI study investigated interaction effects on hippocampal volume between functional genetic variants (*COMT* Val158Met, *BDNF* Val66Met, 5-*HTTLPR*) and environmental adversity in 153 healthy subjects. The variants examined showed significant interactions with environmental adversity with respect to hippocampal volume. The effects of this interaction were additive in nature. Notably, an analysis of hippocampal subfields revealed sub-region-specific volumetric effects for each genetic variant, i.e., 5-*HTTLPR* for the subiculum, *BDNF* Val66Met for CA4/dentate gyrus, and *COMT* Val158Met for CA2/3. The findings indicate that G × E can determine hippocampal volume, which may in turn be relevant to stress-related conditions, including psychotic disorders (Rabl et al., 2014).

Fisher et al. used a large epidemiological case–control sample (172 cases and 246 controls) to explore the interaction between a specific form of childhood abuse and family psychiatric history, in place of specific genetic markers, in the onset of psychosis. The study found no evidence that familial risk accounts for associations between childhood physical abuse and psychotic disorder, or that it substantially increases the odds of developing psychosis among individuals reporting abuse (Fisher et al., 2014).

3.2.1.3. Stress. Several recent studies have evaluated the interactions between candidate genes and stress interaction in psychosis (Modinos et al., 2013). Using a sample of healthy military servicemen, Stefanis et al. (2007) found that compared to *COMT* Met homozygous, *COMT* Val heterozygotes were more prone to a psychotic outcome under stressful conditions (Stefanis et al., 2007).

Similarly, Simons et al. reported that healthy female carriers of the *COMT* Val allele exhibited greater paranoia in response to stress (Simons et al., 2009) However, an opposing interaction was reported by van Winkel et al. (2008) and Collip et al. (2011) who found that stress led to the greatest increase in psychosis in *COMT* Met homozygous patients. Peerbooms et al. (2012) studied an interaction between stress and the polymorphisms in the *COMT* gene (Val158Met) and in the methylenetetrahydrofolate reductase (*MTHFR*) gene (*C677T* and *MTHFR* A1298C) known to differentially affect cognition in patients with schizophrenia and healthy individuals. The authors report that stress reactivity associated with *COMT* Val158Met in patients with psychosis may be moderated by the patient's *MTHFR* C677T genotype. In an investigation of how interaction between polymorphisms in a candidate gene, Neuregulin 1, and psychosocial stress may affect unusual thoughts in patients with schizophrenia, Keri et al. found that compared to C-carriers at rs6994992, T homozygotes had more unusual thoughts in conflict-related conditions (Keri et al., 2009).

Howes and Murray propose that childhood social adversity or similar stressful experiences may interact with genetic predisposition to enhance dopamine synaptic transmission in subcortical areas. The ensuing biased "cognitive schema" predisposes the individual to construe experiences toward paranoid interpretations by misattributing salience to stimuli. Repeated experiences of paranoia and hallucinations exacerbate stress and any associated dopamine dysregulation, eventually solidifying psychotic ideas and beliefs (Howes and Murray, 2014).

3.2.2. Animal studies

There are several approaches to model stressful events in animals, including prenatal stress, maternal separation, isolated rearing or social defeat paradigm (Cryan and Slattery, 2007; Boksa, 2007; Koenig, 2006). A number of recent reviews have described the effects of prenatal and postnatal stress on activity of the hypothalamus–pituitary–adrenal (HPA) axis and resultant behavioral phenotypes (Koenig, 2006; Weinstock, 2008).

3.2.2.1. Reelin. Potential synergistic interactions between maternal separation and genetic risk factors have been studied in reeler mice. Reeler mice are a genetic model of a loss-of-function of *Reelin* (D'Arcangelo, 2005; Costa et al., 2002). The reelin glycoprotein is involved in controlling neuronal cellular interaction as well as migration and positioning (Rogers and Weeber, 2008) Reelin was first implicated in schizophrenia when both mRNA and protein levels of this factor were found to be decreased in temporal and prefrontal cortices, hippocampi and cerebellum in patients (Impagnatiello et al., 1998; Guidotti et al., 2000; Fatemi et al., 2005; Fatemi et al., 2000) although there are negative findings as well (Tochigi et al., 2008). Reelin blood levels were also found to be decreased in schizophrenia and mood disorder patients (Fatemi et al., 2001).

Decreased neuronal levels of reelin were related to increased activity of D-N-methyltransferase (DNMT), suggesting that hypermethylation in the reelin promoter might be responsible for

decreased reelin expression in different layers of the cortex and the white matter (Eastwood and Harrison, 2003; Grayson et al., 2005).

Early maternal separation (PND 2–6) was used to investigate G × E in reeler mice (Laviola et al., 2009). Social motivation was assessed in the 'homing test paradigm' in which 9-day-old mice had to use olfaction to find the nest. Maternal separation was found to reduce social motivation (i.e., increased the latency to reach the nest) in WT but not reeler mice (Ognibene et al., 2007). Further, early maternal separation was associated with reduced social interaction and expression of reelin and BDNF levels in the PFC, striatum and hippocampus in adult WT but not mutants (Ognibene et al., 2008). These reports on reeler mice clearly indicate what appears to be a common theme in many basic G × E studies when two adverse factors (e.g., stress and a genetic variant) might interact in a somewhat unexpected fashion to minimize rather than potentiate each other's effects (Laviola et al., 2009).

3.2.2.2. Nurr1. Another approach to recapitulate aspects of childhood trauma as a schizophrenia risk factor includes social isolation during adolescence. Social isolation of HET *Nurr1* mice during adolescence led to impaired PPI when assessed 12 weeks after the cessation of isolation in adult mice. The behavioral phenotype was associated with decreased tissue content of dopamine (DA) and 3,4-dihydroxyphenylacetic acid (DOPAC) in the PFC in mutants but not in WT animals (Eells et al., 2006), suggesting the synergistic effects. Corticosterone levels were also measured in mutants and controls under the basal conditions and after restraint stress but no group-related differences were detected, arguing that social isolation did not seem to affect stress reactivity in mutant mice (Eells et al., 2006).

3.2.2.3. Sept5. The effects of social isolation were also studied in a mouse model of the *SEPTIN 5* (*SEPT5*) gene. The gene is located within 22q11 region linked to schizophrenia (Harper et al., 2012). *SEPT5* is expressed in the brain both during neurodevelopment and adulthood (Asada et al., 2010) and is involved in vesicular exocytosis by binding to syntaxin in presynaptic SNARE (Soluble N-ethylmaleimide-sensitive factor Attachment Protein Receptor) complexes (Beites et al., 2005). *Sept5* KO mice exhibit decreased social interaction, spent more time in the open arms of the elevated plus maze and showed increased PPI. *Sept5* deletion was also associated with the longer latency to reach the goal in the L maze. However, no differences were observed in spontaneous activity, T-maze, rewarded alternation and tail suspension tests (Suzuki et al., 2009). When *Sept5* KO mice were individually housed after weaning, the amygdalar SEPT5 levels were found to be increased. Compared to group-housed mutants, single-housed ones demonstrated less thigmotaxis in open field, spent more time in the open arms of the elevated plus maze and spent more time in active social interaction compared to group housed mutants, consistent with reduced anxiety levels. This study is another example where adverse factors interact to counteract the negative effects of one another when studied separately (Harper et al., 2012).

3.2.2.4. PACAP. The effects of stress were also studied in mice deficient in pituitary adenylate cyclase activating polypeptide (PACAP). PACAP is a neuropeptide which displays structural similarity to vasoactive intestinal peptide (VIP) and a member of the secretin/glucagon/VIP family. PACAP is involved in circadian rhythms, axonal maturation, axonal integrity and cellular stress responses (Waschek, 2013). PACAP is encoded by the *ADYCAP1* gene located in the 18p11.32 region, a locus linked with schizophrenia (Faraone et al., 2005; Mukherjee et al., 2006; Schwab et al., 1998). Additionally, *ADYCAP1* variants were associated with schizophrenia, deficits in verbal memory and hippocampal volume (Koga et al., 2010). The role of PACAP-DISC1 interaction in neurite outgrowth can be relevant to schizophrenia (Hattori et al., 2007). Mice lacking the *Adycap1* gene do not express PACAP. These mice were subjected to two different rearing conditions, namely a short-term social isolation (SI) at PND 28 or environmental enrichment (EE) starting at PND28 or 56. SI of mutants increased their locomotor activity, decreased latency to attack and increased attacking time in social interaction tests, consistent with elevated aggression. In addition, SI further decreased PPI in mutants. On the contrary, EE at PND 28 but not PND 56 decreased hyperactivity; increased time spent in social interaction tests and decreased duration of immobility in FST. Still, similar to SI, EE worsened PPI in mutant mice (Ishihama et al., 2010). A follow-up study demonstrates that EE for 4 weeks could ameliorate deficits in a contextual fear conditioning test and a novel object recognition test. Intriguingly, these protective effects were still present 2 weeks after cessation of EE even if the brain effects of EE on expression of NMDA receptors, phospho-ERK, phospho-CaMKII, and brain-derived neurotrophic factor (BDNF) were no longer observed. The results suggest that the EE-induced molecular changes in the hippocampus might be required for initiation but not maintenance of long-lasting effects of EE on cognitive function (Takuma et al., 2014).

3.2.2.5. DISC1. Recently, a dominant negative mouse model with expression of mutant DISC1 under the PrP promoter was used to study synergistic effects of the mutation and social stress. Mutant and control were exposed to 3-week isolation beginning from 5 weeks of age. It was found that only mutants exposed to SI displayed increased locomotor activity, deficient PPI, and increased immobility in FST, suggesting G × E effects. These effects were associated with decreased extracellular levels of dopamine and TH expression, increased D2R expression in the frontal cortex and increased DA levels in the NAc, the main forebrain targets of DA projections of the ventral tegmental area. The authors also report increased levels of corticosterone in SI challenged mutants and were able to reverse the effects of SI with the glucocorticoid receptor antagonist, mifepristone. SI-increased glucocorticoids production resulted in methylation of the TH promoter, leading to reduced TH expression selectively in the mesocortical pathway. This reduction was also reversed with mifepristone. This study provides an example of the convergent target of G × E relevant to schizophrenia (Niwa et al., 2013). Mice carrying *Disc1* point mutations were exposed to chronic social defeat (CSD). CSD were applied to Q31L or L100P mutants during PND 50–70 followed by behavioral testing. CSD increased time spent in open arms of the elevated plus maze in Q31L/+ mice while significantly decreasing the same in L100P/+ mice. CSD also decreased PPI and increased sociability and social novelty in L100P/+ mutants, suggesting an interactive effect (Haque et al., 2012).

3.2.2.6. GAD. Stress influences the development and function of GABAergic neurons (Fine et al., 2014). Glutamic acid decarboxylase (GAD) is the enzyme responsible for conversion of glutamate to GABA. GAD is coded by *GAD1* located within 2q31.1 region. Initial studies have revealed decreased expression of GAD, specifically the *GAD67* isoform, in the PFC of schizophrenia subjects (Akbarian et al., 1995; Volk et al., 2000). Subsequent studies demonstrated that this reduction was mainly related to Parvalbumin-positive interneurons (Curley et al., 2011; Kimoto et al., 2014; Volk et al., 2012; Beneyto et al., 2012). Additionally, the levels of the enzyme that methylates the promoter of *GAD67* to decrease its expression were elevated in PFC interneurons of psychosis patients (Veldic et al., 2007). Prenatal stress was applied in an animal model using knock-in (KI) mice that express GFP with endogenous *Gad67* promoter to label *Gad67* expressing interneurons (Tamamaki et al., 2003). Heterozygous mice express *Gad67* in one allele (*Gad67*+/GFP) and can be

considered as a knock-down model in which the total expression of *Gad67* is half of the WT level (Tamamaki et al., 2003). Restraint-and-light stress at GD17 increased maternal cortisol levels in both WT and *Gad67*+/GFP mothers, with mutant having a greater increase. Fetal body weight was significantly reduced and fetal cortisol levels were much higher in the mutant fetuses exposed to stress (Uchida et al., 2011). In a follow-up study, mutant mice were exposed to restraint-light stress during GD 15–17.5. This intrauterine exposure was associated with the decreased number of parvalbumin positive interneurons in the PFC, somatosensory cortex and hippocampi of mutant offspring only (Uchida et al., 2014).

3.2.2.7. SNAP25. A similar paradigm was used in Bdr mice that expresses a defective SNAP25 protein that alters its binding to SNARE complex and affects presynaptic vesicular exocytosis (Jeans et al., 2007). Synaptosomal-associated protein-25 (SNAP25) is a presynaptic protein that takes part in vesicular exocytosis (Chen and Scheller, 2001), neurite outgrowth (Wu et al., 2011) and long-term potentiation (Jurado et al., 2013) Evaluation of synaptic proteins in the post-mortem samples revealed altered SNAP25 levels in the frontal and temporal lobes (Karson et al., 1999; Thompson et al., 1998), and also in the entorhinal cortex (Young et al., 1998), hippocampus (Fatemi et al., 2001; Thompson et al., 2003) and cerebellum (Mukaetova-Ladinska et al., 2002) of schizophrenia patients. Additional evidence for the role of SNAP25 came from relatively small scale genetic epidemiologic studies, some of which reported positive association with *SNAP25* variants and schizophrenia (Carroll et al., 2009; Lochman et al., 2013) but negative studies also exist (Kawashima et al., 2008; Dai et al., 2014). Bdr mice displayed ataxia (hence blind-drunk), PPI impairment, reduced social interaction and exploratory behavior (Jeans et al., 2007). Circadian rhythm impairment, namely phase advance in the sleep pattern, as well as altered blood corticosterone and arginine-vasopressin levels were observed in these mice (Oliver et al., 2012). Prenatal stress decreased time spent with another mouse (as a sociability index) and decreased time spent with a novel stranger mouse (as a social novelty index) in Bdr mice only. Stressful treatment of Bdr and control mice resulted in reduced PPI that could be ameliorated with antipsychotics (Oliver and Davies, 2009).

3.2.2.8. NRG1. A different model of a candidate genetic risk factor, Neuregulin 1 (*NRG1*), was also evaluated with regard to a putative interaction with cannabis. The association of *NRG1* and schizophrenia was first suggested in a large Icelandic sample (Stefansson et al., 2002). Follow-up epidemiologic studies reported both positive and negative associations of different *NRG1* variants and schizophrenia (Iwata et al., 2004; Li et al., 2014; Stefansson et al., 2003; Thiselton et al., 2004; Williams et al., 2003). In some postmortem studies *NRG1* signaling components have been found increased in schizophrenic patients (Chong et al., 2008; Hahn et al., 2006; Hashimoto et al., 2004). *NRG1* plays an important role in neuronal migration, axonal guidance, neuronal and glial maturation, myelination and synaptogenesis. *NRG1* mutations are associated with impairments in glutamatergic, dopaminergic and GABAergic neurotransmission (Li et al., 2007; Newell et al., 2013). With regard to the pathogenesis of schizophrenia, increased NRG1 signaling is proposed to lead to increased GABAergic inhibition of glutamatergic pyramidal neurons, resulting in a hypoglutamatergic state (Mei and Xiong, 2008; Deng and Dean, 2013; Mei and Nave, 2014). The *Nrg1* KO homozygosity has a fatal effect on mice. In a heterozygous state, there were no gross differences in the appearance of the mice and, behaviorally, the mutant mice displayed increased spontaneous activity and deficit in PPI (Golub et al., 2004).

A *Nrg1*-transmembrane-domain knockout mice exhibited increased locomotor activity, decreased PPI, impaired social novelty, and increased sensitivity to NMDAR antagonists in their heterozygous state (O'Tuathaigh et al., 2007; O'Tuathaigh et al., 2010; Stefansson et al., 2002). These mice were utilized in studies for several different types of G × E. *Nrg1* HET mice were exposed to CSD starting on PND 35. When evaluated in adulthood, CSD decreased locomotor activity, numbers of alternation in Y-maze, decreased the proportion of time spent with a novel subject in a social interaction test and increased the number of walkovers in social investigation in *Nrg1* mutant mice. Analyses for selected immunological variables were carried out and revealed that CSD in mutants differentially increased the levels of basal cytokines and caused variable changes in IL1β and TNFα levels in different brain regions (Desbonnet et al., 2012).

Nrg1 transmembrane heterozygous mutants were exposed to acute restraint stress in two different periods, younger (3–4 months) and older (6–7 months) ages. Stress reduced locomotor activity and exploratory behavior in both groups of mice. However, additive genotype–stress interaction only occurred in older mice. In particular, mutants did not display anxiety-like behavior in the open field while WT mice did. Contrary to the behavioral test results, corticosterone response to stress was more pronounced in younger mice (Chesworth et al., 2012). In a different study, the authors applied a subchronic restraint stress paradigm during adolescence (PND 36–49, 30 m/day). Repeated, but not acute, stress caused disruption in PPI only in the stressed-mutant group. Acute and repeated stress resulted in increased levels of corticosterone levels, however the response was significantly less in the mutants after repeated stress. Interestingly stress decreased apical dendritic length and complexity in the medial prefrontal cortex and hippocampus of the mutants (Chohan et al., 2014a). NMDA receptor binding of MK-801 was increased but the response was blunted in the ventrolateral septum, more pronounced in the dentate gyrus, and binding was decreased in the inferior-lateral region of the mPFC of the mutants (Chohan et al., 2014b).

The effects of stress were also evaluated in genetic models created in genetically modified rats. A rat model was created by disrupting the 5′ region of *Nrg1*. This genetic manipulation produced decreased type II NRG1 mRNA and protein expression. The mutants displayed deficient habituation in the open field, impaired memory in visuo-spatial discrimination and cued fear conditioning (Taylor et al., 2011, 2012). When these animals were exposed to a chronic variable stress paradigm at PN37 through 44, both mutant and WT rats displayed less anxiety-related behavior. As an indication of sex-specific effects of G × E, only mutant females showed enhanced cued-fear extinction following stress exposure (Taylor et al., 2013). A further discussion of different *NRG1* models can be found in a review by Karl (2013).

Similar to the immune models, the weaknesses of the G × E stress models include lack of time- and dose-dependent effects of stressful factors. There have been very few if any studies of pathogenic factors that can be activated by stress in addition to glucocorticoids, e.g., immune factors or markers of oxidative stress. There is still a limited examination of epigenetic modifications following developmental exposure of genetically modified animals to stressful conditions. At a more fundamental level, modeling stressful exposures relevant to human conditions remains a challenge given that some stressful events appear to be uniquely human, e.g., sexual and physical child abuse or urban settings. Although some approaches to mimic urban upbringing have been described (e.g., Lambert et al., 2015).

3.3. Substance abuse

3.3.1. Human studies

3.3.1.1. Cannabis. The cannabis plant, *Cannabis sativa*, contains more than 60 cannabinoids (Brenneisen, 2007). The main

psychoactive component of cannabis is Δ9-tetrahydrocannabinol (THC). THC exerts its psychoactive effects such as relaxation, confusion, anxiety, and effects on memory through cannabinoid 1 (CB1) receptors that are widely expressed in the central nervous system, most prominently in the basal ganglia, cerebellum, hippocampus and the cortex (Wachtel et al., 2002; D'Souza et al., 2004; Pertwee, 2008; Wong et al., 2010). Notably, another major compound found in the cannabis plant, cannabidiol (CBD), is thought to be responsible for potentially medically beneficial applications including anxiolytic, anti-depressive, anti-psychotic and anti-convulsive effects (de Mello Schier et al., 2014; Devinsky et al., 2014; Iseger and Bossong, 2015). CBD may act as a CB1/CB2 inverse agonist by antagonizing endogenous cannabinoids, anandamide and 2-arachidonoylglycerol, e.g., inhibiting degradation of anandamide (Bisogno et al., 2001; Pertwee, 2008). CBD is suggested to possess antipsychotic properties as well as the ability to reverse the acute effects of THC (Iseger and Bossong, 2015; Schubart et al., 2014). Still, the data on clinical efficacy of CBD are still limited and more studies are clearly needed to conclusively support the beneficial role of the compound (McLoughlin et al., 2014).

Long-term heavy cannabis use during adolescence has been associated with increased risk of schizophrenia (Andreasson et al., 1987; Arseneault et al., 2002; Fergusson et al., 2005; van Os et al., 2002; Evins et al., 2012; Radhakrishnan et al., 2014). Epidemiologic data suggest that an early use of cannabis is associated with an earlier onset of schizophrenic symptoms (Barnes et al., 2006), and cannabis use is also increased in patients years prior to the diagnosis (Boydell et al., 2006). Still, the causative role of cannabis use in schizophrenia risk remains unclear. One suggestion is that heavy cannabis use during adolescence may have particularly detrimental effects on cognition and brain development in vulnerable individuals (van Os et al., 2003).

The polymorphism in the *COMT* gene, *COMT* Val158Met, was demonstrated to moderate the effects of cannabis use on adult psychosis. In particular, Val allele carriers were more prone to develop psychosis in the presence of adolescent cannabis use (Caspi et al., 2005; Henquet et al., 2006, 2009). However, negative results for the association were also reported (Costas et al., 2011; Zammit et al., 2007; Kantrowitz et al., 2009). *AKT1* is another candidate gene in which mutations may be associated with cognitive and behavioral symptoms in cannabis users. *AKT1* is known to play a role in apoptosis, cellular migration, transcription and cell proliferation (Staal et al., 1977). The initial study identifying *AKT1* mutations as a risk factor assessed 152 SNPs in 46 genes, determined by a hypothesis driven approach. In both patients with disease and at-risk individuals, *AKT1* rs2494732 polymorphisms indicated interaction with cannabis use toward the generation of psychotic symptoms. In particular, a C/C genotype was associated with psychosis, and the risk increased with higher cannabis consumption (van Winkel and GROUP Investigators, 2011). *AKT1* rs2494732 was also associated with cognitive impairment increased by heavy cannabis use, with C/C genotype carriers having decreased accuracy and longer reaction times in the continuous performance test (van Winkel et al., 2011). The interaction of *AKT1* rs2494732 with cannabis in schizophrenia was confirmed in a case–control study, which displayed a dose-dependent increase in psychosis risk among cannabis users (Di Forti et al., 2012). Another study found a cannabinoid receptor 1 polymorphism, rs12720071, associated with smaller fronto-temporal white matter volume in schizophrenia patients also using cannabis (Ho et al., 2011). This work provides additional evidence for the interactive effect of cannabis and genetic background on morphological alterations in schizophrenia.

In a magnetic resonance imaging (MRI) study in 47 first-episode schizophrenia patients and 30 healthy control subjects, Malchow et al. investigated effects of previous cannabis abuse and increased familial risk on the hippocampus, amygdala, caudate nucleus, putamen, thalamus and sub-segments of the corpus callosum. In a subsequent single-volume ^{1}H magnetic resonance spectroscopy study, they also analyzed spectra in the left hippocampus and putamen to detect metabolic alterations. Patients with a family history of schizophrenia combined with previous cannabis abuse, showed lower volumes of the bilateral caudate nucleus compared to all other patients, implicating an interaction between the genetic background and cannabis abuse (Malchow et al., 2013). In a sample of 2082 healthy individuals, Power et al. show an association between an individual's inheritance of schizophrenia risk alleles and use of cannabis. This was significant for comparing those who have used cannabis compared to those who have never used it. These findings suggest that a portion of the association between schizophrenia and cannabis appears to be linked to a potential genetic predisposition toward use. This research exemplifies a form of gene–environment correlation within this system (Power et al., 2014).

The effects of cannabis' use were also associated with another candidate gene for schizophrenia, Neuregulin-1 (*NRG1*). Cannabis-derived compounds were found to be associated with alterations in the electrophysiological markers related to schizophrenia, such as mismatch negativity (MMN) and p300 (Juckel et al., 2007; Roser et al., 2008). In particular, acute administration of THC reduced p300 amplitude in a way similar to that seen in schizophrenia patients, while cannabis extract, which also includes CBD, increased the amplitude of auditory evoked MMN. THC administration was associated with a reduced MMN amplitude in people carrying *NRG1* rs7834206C/C genotype (Stadelmann et al., 2010). Notably, a recent GWA study identified a *NRG1* variant, rs17664708, as a risk allele for the development of cannabis dependence in Americans of both African and European descent (Han et al., 2012).

3.3.1.2. Methamphetamine. Methamphetamine (METH) induced psychosis, a concept that originated in Japan following an epidemic of methamphetamine abuse there in the 1950s, was described as a long-lasting psychotic syndrome precipitated by METH associated brain damage (Sato, 1992). Following further peaks of METH abuse in the 1980s and 90s, the characteristics of the syndrome were redefined as progressive impairment in mental and cognitive status with repeated use, and vulnerability to relapse of psychotic symptoms, with a long duration for this vulnerability (Ujike and Sato, 2004). A series of studies from Australia also evaluated the association between METH use and psychotic symptoms. A face-to-face interview method was applied to 309 self-reported recreational users (McKetin et al., 2006). Psychotic symptoms were found in almost one-fourth of the users and METH use increased the odds of psychotic symptoms three times (OR 3.1, 95% CI 1.6–5.9). A follow-up cross sectional survey also revealed that METH use was associated with the occurrence of psychotic symptoms. More than 80% of those who had experienced at least two psychotic symptoms in the past year reported the concurrent use of METH (McKetin et al., 2010). In a larger sample, active METH use was associated with the severity of psychotic symptoms. METH use lasting more than 2 weeks during the preceding month increased the odds of psychotic symptoms more than 11 times (OR 11.2, 95% CI 5.9–21.1). In this study, comorbid cannabis and alcohol use also increased the risk of psychotic symptoms almost two fold (McKetin et al., 2013). However, these studies do not differentiate the acute effects of METH use from chronic ones; therefore they may not be supportive of the syndrome as described by Japanese researchers.

Similar to cannabis use, G × E may play a role in the genesis of METH-associated psychosis. It is likely that some individuals are

more vulnerable to developing psychotic symptoms than others and it is also plausible to suppose that their genetic backgrounds may explain this susceptibility. Because of the previously described history, the majority of genetic association studies in this system were reported from Japan. Briefly, those genetic association studies found positive association between METH induced psychoses and certain haplotypes of neurotransmission associated genes. These genes included dopamine β-hydroxylase (Kalayasiri et al., 2014), dopamine transporter (Ujike et al., 2003), dopamine receptor 2 (*DRD2*) (Harano et al., 2004), *DRD4* (Chen et al., 2004), *COMT* (Jugurnauth et al., 2011; Suzuki et al., 2006), glycine transporter-1 (Morita et al., 2008), *PICK1* (Matsuzawa et al., 2007), *G72* (Kotaka et al., 2009), *GRM2* (Tsunoka et al., 2010), *GRIN1* (Chanasong et al., 2013), Serotonin transporter (*5- HTTLPR*) (Ezaki et al., 2008), serotonin 1A receptor (Kishi et al., 2010), serotonin 6 receptor (Kishi et al., 2011) and monoamine oxidase-A (Nakamura et al., 2009). Additional associations have been seen with various other genes such as alpha-synuclein (in females only) (Kobayashi et al., 2004), glutathione-S-transferase (Hashimoto et al., 2005; Hashimoto et al., 2008), quinone oxireductase (Ohgake et al., 2005), dysbindin (Kishimoto et al., 2008a), frizzled-3 (Kishimoto et al., 2008b), estrogen receptor alpha gene (Kishi et al., 2009), and neuropeptide Y1 receptor (Okahisa et al., 2009). However, the G × E picture in METH associated psychosis is inconsistent for several of these genes (Chen et al., 2004; Hosak et al., 2011; Liu et al., 2004). Finally, a recent study revealed that the risk alleles for METH-induced psychosis were enriched in the schizophrenia GWAS dataset (Ikeda et al., 2013).

3.3.2. Animal studies

3.3.2.1. COMT. Clinical and preclinical studies have indicated that genes encoding proteins of dopamine signaling contribute to the cannabis-psychosis association (O'Tuathaigh et al., 2014). As COMT (catechol O-methyl transferase) degrades dopamine, the putative role of COMT in pathogenesis of schizophrenia has been extensively evaluated. In addition to its functional role, the genomic location of *COMT* (22q11.21) also points to the role of this enzyme in schizophrenia (Gothelf et al., 2014; Paterlini et al., 2005) given that individuals with 22q11 deletion syndrome carry the higher risk of psychosis (Karayiorgou et al., 1998; Murphy et al., 1999). The discovery of val158met functional polymorphism (rs4680) has fueled the research in the role of this polymorphism in the development of psychosis, and regulation of affect and cognition (Heim et al., 2013; Nixon et al., 2011; Ucok et al., 2010; Wirgenes et al., 2010). Comt deficient mice were produced almost two decades ago (Gogos et al., 1998).

Homozygous mice have no COMT activity and increased levels of 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), with no changes in striatal, cortical or hypothalamic content of DA or noradrenaline (NA) (Huotari et al., 2002). By using rapid-time sampling behavioral checklist technique, the ethogram of these mice was studied in detail. Heterozygous mutants displayed increased sifting and chewing, and reduced 'free' rearing (Babovic et al., 2007). Spontaneous locomotion of mutants did not differ from that of controls, although male mutants displayed increased locomotor activity after acute amphetamine injection (Huotari et al., 2004).

In order to evaluate possible effects of G × E, *Comt* HET mice were exposed to chronic adolescent THC at PND 32–52. Adolescent THC exposure decreased density and soma size of the ventral tegmental area (VTA) dopaminergic cells (Behan et al., 2012). A follow-up study assessed the effects of chronic adolescent exposure to the cannabinoid receptor agonist, WIN 55212, in COMT mutants. The agonist was administered at PND 32–52, and the behaviors were assessed 21 days later. The agonist increased the startle response, decreased PPI and increased time spent in light area in light/dark test in mutant mice. Notably, the COMT inhibitor, tolcapone, reversed these effects of the agonist, consistent with the notion that at least some of the behavioral effects of the agonist were mediated by DA metabolism regulated by COMT (O'Tuathaigh et al., 2012).

3.3.2.2. NRG1. An Australian group has studied the effects of THC on *Nrg1* transmembrane HET mice. 48–84 week-old WT and HET *Nrg1* KO animals were given a battery of behavioral tests after acute administration of THC in the dose of 5 and 10 mg/kg. Without THC exposure, *Nrg1* HET mice showed less aversion to light in the light–dark box. They also spent more time in the open arms during elevated-plus maze testing and showed general hyperactivity. In only *Nrg1* heterozygous mutants but not in controls, THC reduced locomotor activity, decreased time spent in open arms, increased aversion to the light area, changed PPI and altered the neuronal activity pattern as measured by c-fos expression in the lateral septum (Boucher et al., 2007). Long-term cannabis administration was modeled in *Nrg1* transmembrane domain mutant mice. Mice were treated with THC from PND 21 to 32 and a comprehensive evaluation was carried out at adulthood. Unexpectedly, THC administration resulted in a decrease in hyperactivity in mutant mice. The reduction in sniffing (an index of social interaction) observed in control mice treated with THC was not evident in *Nrg1* mutants. Chronic THC administration increased CBR1 binding in *Nrg1* mutants and affected 5HT2A binding (Long et al., 2013). Tolerance to some of the effects of cannabinoids was modulated by neuregulin-1 in a repeated cannabinoid administration model. The effects of repeated CP55,940, a THC analogue, on thermoregulation and locomotor activity was abolished in neuregulin-1 mutants, however anxiogenic effects remained stable in the mutants and improved in WT mice (Boucher et al., 2011). Same mutants were also administered CBD in variable doses and the mice were tested at different time periods. Long-term treatment of CBD at high doses reduced the hyperlocomotion and increased social interaction in *Nrg1* TM HET mutant mice, however anxiolytic-like effects were only seen in WT. Acute but not chronic administration of high-dose CBD improved PPI. There were slight differences in the binding patterns of 5- HT2A and GABAA receptors between the mutants and the WT mice (Long et al., 2012).

3.3.2.3. DISC1. We have recently reported that a perturbation in DISC1 expression exacerbates the response to adolescent exposure to THC. We demonstrated that chronic adolescent treatment with THC intensified deficits in fear-associated memory in adult mice that express a putative dominant-negative mutant of DISC1 (DN-DISC1). A synergistic reduction of c-Fos expression induced by cue-dependent fear memory retrieval was found in DN-DISC1 THC-treated mice. These results suggest that mutant *Disc1* could contribute to the detrimental effects of adolescent cannabis exposure (Ballinger et al., 2015).

A similar but inducible DN-DISC1 model was used to evaluate putative effects of chronic methamphetamine administration. In order to mimic a pattern of human methamphetamine abuse, a non-toxic, gradually escalating dose regimen (ED) was used. Specifically, METH doses were gradually increased over a 2-week period. Mutant *Disc1* mice exhibited a blunted METH-induced locomotor sensitization and attenuated conditioned place preference in female mice. We also found decreased DA D2 receptor binding and altered AKT/GSK3 signaling in the ventral striatum in female mutant *Disc1* mice. These findings suggest that DISC1 signaling may be involved in the neurobehavioral changes induced by psychostimulants, potentially moderating their contribution to schizophrenia (Pogorelov et al., 2012).

The main weakness of all G × E drug studies is the lack of behavioral paradigms that would more accurately mimic human drug use, i.e., drug self-administration. Use of contingent paradigms could also help uncover common molecular pathology of drug abuse and other major psychiatric disorders that are often co-morbid (Volkow, 2004).

3.4. Obstetric complications

Obstetric complication has been long known as a risk factor for schizophrenia (Schmidt-Kastner et al., 2012; Mittal et al., 2008; Suvisaari et al., 2013; Forsyth et al., 2013; Walshe et al., 2011).

3.4.1. Human studies

A meta-analysis conducted with data derived from 2 prospective studies in 2002 revealed that the biggest risk factor was gestational diabetes, with an OR of 7.76, 95% 1.37–43.90 (Hultman et al., 1999; Jones et al., 1998). This is followed by factors such as birth weight under 2000 g, emergency cesarean section, congenital malformations, uterine atony, rhesus incompatibility, asphyxia, bleeding in pregnancy, and preeclampsia (Cannon et al., 2002a). Overall obstetric risk factors determined from prospective studies show moderate effects on schizophrenia risk, with OR between 1.5 and 2 (Cannon et al., 2002b). Some of these factors are associated with fetal hypoxia, such as neonatal cyanosis, apnea and required resuscitation, suggesting the possibility of common underlying mechanisms of pathogenesis. Obstetric complications may also be associated with adverse brain abnormalities, including the lateral ventricle enlargement (Bersani et al., 2009). For a more detailed overview of obstetric complications in schizophrenia, the readers are referred to the review by Mittal et al. (2008).

Further research in the field has emerged on the interaction of obstetric complications and genetic liability for schizophrenia. In familial cases, having two parents with schizophrenia compared to one parent-only or healthy controls, increased the magnitude of lateral ventricle enlargement in the presence of obstetric complications (Cannon et al., 1993). Patients who were exposed to hypoxia had reduced gray matter and decreased CSF volume compared to their siblings, who also were seen to have smaller volume than controls (Cannon et al., 2002c). Van Erp and colleagues found that schizophrenia patients who had experienced hypoxia had smaller hippocampal volumes than those who had not, or their siblings and controls, demonstrating enhanced effects of hypoxia on genetically vulnerable individuals (Van Erp et al., 2002). In a similar association, patients with a family history of schizophrenia had enlarged lateral ventricles, and this enlargement was not observed in non-familial cases (McDonald et al., 2002).

Nicodemus and colleagues tested potential interactions between schizophrenia candidate genes regulated by hypoxia or involved in vascular function in the brain (*AKT1*, *BDNF*, *CAPON*, *CHRNA7*, *COMT*, *DTNBP1*, *GAD1*, *GRM3*, *NOTCH4*, *NRG1*, *PRODH*, *RGS4*, *TNF-alpha*) and serious obstetric complications. A family-based study of transmission disequilibrium was conducted in 116 trios. Despite the small sample size and limited power of analysis, *AKT1* (three SNPs), *BDNF* (two SNPs), *DTNBP1* (one SNP) and *GRM3* (one SNP) showed significant gene–environmental interaction. The findings are consistent with the hypothesis that genes involved in neurovascular function, or regulated by hypoxia, could interact with obstetric complications to increase the risk for schizophrenia (Nicodemus et al., 2008).

Another study found that rs2518824 polymorphism of the *ARVCF* gene, which is deleted in 22q11 syndromes, and rs174576 SNP in the fatty acid desaturase 2 gene, a rate-limiting synthetic enzyme for endogenous long chain polyunsaturated fatty acids, were both associated with white matter abnormalities in preterm infants. These results suggest that genetic variants may influence the effects of preterm birth on white matter development (Boardman et al., 2014). Severe fetal hypoxia was associated with smaller volume of the hippocampus in schizophrenia patients, and this pathology correlated with rs13242038 polymorphism in the *GRM3* gene (Haukvik et al., 2010). Given these findings, Geoffroy et al. emphasize a growing need to apply neuroimaging studies on cases involving G × E associations already known to have a clinical effect, such as infections, early stress, urbanicity, and substance abuse (Geoffroy et al., 2013).

3.4.2. Animal studies

There are several approaches to model obstetric complications in animal (Boksa, 2004). Among most popular models are those that include diabetes during pregnancy and encompass systemic administration of streptozotocin (an agent cytotoxic to pancreatic B cells) and those utilizing alloxan-induced diabetes or hyperglycemia produced by glucose administration. Another pathological condition, preeclampsia, can be modeled using acute administration of low doses of bacterial endotoxin, long-term nitric oxide synthase (NOS) inhibition, and aortic co-arctation. Perinatal hypoxia, as a common pathogenic factor for several obstetric complications, can be reproduced in animals with global anoxia during a C-section birth (Boksa, 2004).

There have been very few studies of how genetic factors can modulate the brain and behavior effects of obstetric complications. For example, Berger et al. (2000) compared the effects of vaginal and C-section birth on amphetamine (AMPT)-induced locomotor activity in different strains of rats. Amphetamine-induced locomotion was increased in Sprague-Dawley rats and reduced in Lewis rats after C-section birth as compared to vaginal birth. It was suggested that C-section might produce differing long-term changes in dopaminergic function, depending on the genetic composition of the individual. A different approach was taken by Wakuda and colleagues. They examined the effects of hypoxia on expression of schizophrenia genetic risk factors. They found that a 15-min exposure to intrauterine anoxia during cesarean section birth altered expression of *Nrg1* and *Comt* mRNA in the prefrontal cortex but not the hippocampus at 6 and 12 weeks after birth (Wakuda et al., 2015).

3.5. Environmental toxins

3.5.1. Human studies

Although the putative role of environmental toxins in schizophrenia is only now becoming a focus of epidemiological and basic research, the detrimental effects of neurotoxins on brain and behavior have been convincingly demonstrated. For example, prenatal organophosphates exposure has been linked to neurocognitive impairment and is used in G × E modeling of abnormal neurodevelopment (Whyatt and Barr, 2001). Chlorpyrifos (CPF) is an organophosphate pesticide that might induce behavioral disturbances after intrauterine exposure, suggested by epidemiological (Whyatt and Barr, 2001) and animal data (Levin et al., 2002).

Recent evidence suggests a potential association between prenatal lead (Pb^{2+}) exposure and schizophrenia (Guilarte et al., 2012; Opler et al., 2004, 2008; Opler and Susser, 2005). Although the epidemiological evidence for this association is relatively weak, there is the strong biological plausibility for the putative link as both schizophrenia and developmental Pb^{2+} exposure are characterized by hypoactivity of the N-methyl-D-aspartate receptors (NMDAR) (Guilarte, 2009).

3.5.2. Animal studies

3.5.2.1. Reelin. Chlorpyrifos (CPF) is an organophosphate pesticide that might induce behavioral disturbances after intrauterine

exposure, suggested by epidemiological (Whyatt and Barr, 2001) and animal data (Levin et al., 2002). It was hypothesized that a deficiency in reelin may affect the compensatory changes following early CPF exposure. Pregnant HET reelin females were exposed to CPF to assess the effects on neurobehavioral development of the offspring. Decreased ultrasonic vocalization (USV) as a measure of communication in mice (Scattoni et al., 2009) was "restored" to WT levels in CPF exposed reeler mice when measured at PND 7. Similar modulatory effects of CPF exposure were found with regard to amphetamine-induced hyperactivity and increased stereotypy (Laviola et al., 2006). The behavioral effects of CPF were associated with the brain changes in the olfactory bulb and the cerebellum in reeler mice (Mullen et al., 2013). On the one hand, these findings may be relevant to cholinergic abnormalities in autism and schizophrenia (Laviola et al., 2009). On the other hand, the above studies again demonstrate how adverse effects of environmental toxins could become paradoxical when combined with genetic variants.

3.5.2.2. DISC1. In order to experimentally test this hypothesis, we investigated the effects of prenatal exposure to Pb^{2+} in mutant *Disc1* mutant mice (Abazyan et al., 2014; Guilarte, 2009). The experimental groups of mice were fed with moderate levels of Pb^{2+} containing diet throughout their lifetime while the control group received non-Pb^{2+} containing diet. Male mutant *Disc1* mice exposed to Pb^{2+} displayed increased peripheral activity and decreased rearing. Pb^{2+} decreased the time spent in open arm in both mutants and controls consistent with increased anxiety-like behavior. In both female and male mice, Pb2+ exposure and mutant *Disc1* additively increased locomotor activity induced by the NMDA receptors antagonist, MK-801.

Since Pb^{2+} plays a role in vesicular exocytosis and high doses alter the structure and formation of NMDA containing synapses (Neal et al., 2010, 2011), we attempted to rescue the effects of Pb^{2+} by administering a NMDAR co-agonist, D-serine. D-serine is an allosteric modulator of NMDAR and has been used in translational studies as well as in clinical trials (Kantrowitz et al., 2010; Labrie and Roder, 2010; Yang and Svensson, 2008). DISC1 binds serine racemase (SR), the enzyme producing D-serine and mutant *DISC1* decreases D-serine production by altering the binding properties of SR (Ma et al., 2013). Administration of D-serine was able to rescue the effects of Pb^{2+} on PPI (Abazyan et al., 2014). The results seem to support the hypothesis that some environmental neurotoxins may be able to contribute to the pathogenesis of schizophrenia or related mental illnesses via interacting with genetic liability in susceptible individuals.

The main drawbacks of the G × E environmental studies are related to insufficiently accurate methods of exposure to different environmental pollutants, limited studies of time- and dose-dependent effects of neurotoxins, lack of analyses of systemic and whole-body abnormalities that could contribute to behavioral pathology independently of the brain effects. Further, more epidemiological studies are clearly needed to better understand if environmental pollutants play a role in the pathogenesis of schizophrenia.

4. Summary

Recent epidemiological studies have advanced our understanding of the putative mechanisms of G × E relevant to psychotic disorders, particularly related to genetic interactions with cannabis, stress and immune dysfunction (Modinos et al., 2013; Khandaker et al., 2014). Generally, G × E research in schizophrenia has used candidate genes-based approaches. Recent reviews of the topic have indicated several fundamental problems with those approaches, including insufficient sample sizes, statistical artifacts and publication biases (Duncan and Keller, 2011; Iyegbe et al., 2014). Even if these G × E findings are plagued with inconsistent results, they have provided the initial guidance for follow-up experimental research in animal models that are better poised to identify the underlying biological mechanisms, whereby environmental and genetic risk factors interact to cause psychiatric disease (Iyegbe et al., 2014). Progress in psychiatric genetics and epidemiology has facilitated the development of animal models that combine genetic and environmental factors relevant to schizophrenia. This has allowed for an exciting opportunity to model the complex interactions between different factors implicated in the disorder. Tables 1 and 2 summarize the reviewed human research on and animal models of G × E in schizophrenia.

Here, we try to summarize the recent G × E animal studies. Fig. 1 presents a few examples of the major outcomes of G × E effects in mouse models published within the last decade. Although synergistic effects remain a major outcome of G × E, we now appreciate that this is not the only result of G × E despite expectations mostly influenced by the two-hit hypothesis (Bayer et al., 1999; Maynard et al., 2001; Feigenson et al., 2014). It is not rare to see that combining a genetic mutation and an environmental stressor results in emergence of neurobehavioral phenomena that suggest "protective" effects of the combination. There are now several examples when modeling G × E in mutant mice with some pre-existing abnormalities gives rise to phenotypes that are not observed in challenged control mice or unchallenged mutant animals. One should anticipate such results by designing G × E experiments to avoid a trap of a limited set of pre-planned tests used to "capture" specific disease-related alterations. Appearance of new brain and behavioral changes, particularly while using the genetic mutation implicated in various psychiatric conditions, could inform us about the role of environment in bringing about diverse clinical outcomes in patients with the same mutation. The Scottish pedigree with the disruption of *DISC1* due to the chromosomal defect is an example of such a possibility (Blackwood et al., 2007). Variability of phenotypic outcomes of G × E in animal models is congruent with heterogeneity in normal and abnormal human behaviors observed in G × E studies (e.g., Grishkevich and Yanai, 2013). We suggest that abandoning the idea of modeling the entire disorder and focusing on more tangible and biologically meaningful endophenotypes and dimensions may help overcome the issue of heterogenic outcomes and inconsistency in G × E research. However, before describing this idea in details, we briefly overview the field of animal models of psychiatric disorders.

5. Future prospects

McKinney and Bunney (1969) proposed criteria for a model of a psychiatric disease. A valuable animal model should demonstrate analogy of symptoms, observable and measurable behavioral changes, consistency between observers, and similarity in responses to treatments. Willner (1984) formalized the criteria of validity and proposed that face, predictive, constructive and etiological validity are the foundation criteria. Face validity models are defined as those that recapitulate individual symptoms of a disorder. In case of schizophrenia, behavioral similarities can be difficult to obtain, as the key symptoms of the disorder, e.g., hallucinations or delusions are of an exclusively human nature. Even when schizophrenia-related behaviors such as hyperactivity or impaired pre-pulse inhibition (PPI) of the acoustic startle are modeled, it is often unclear whether they arise from pathogenic processes relevant to schizophrenia. This is because hyperactivity, for example, can be induced by numerous experimental manipulations. It is not uncommon to encounter publications that

Table 1
Selected positive G × E interactions obervered in human cases of schizophrenia.

Genetic variant	Environmental factor	Outcomes	References
MHC (rs1051788)	Infection	Positive association between MHC SNP and seropositivity for CMV and HSV-1. SNP also associated with reduced PFC volume in SCZ patients	Shirts et al. (2007) Prasad et al. (2010)
IL18R	Infection	Positive association between IL-18r SNP and seropositivity for HSV-1/2, and CMV in SCZ patients	Shirts et al. (2008)
CTNNA3 (rs7902091)	Infection	Association between SCZ exposure and genotype only found in combination with CMV exposure	Borglum et al. (2014)
GRIN	Maternal infection	Maternal HSV-2 exposure linked to GRIN2B genetic variation, encoding for NMDAR subunits	Demontis et al. (2011)
HLA-DR1	Season of birth	Association between winter birth and HLA-DR1 genotype in SCZ patients	Narita et al. (2000)
HLA-A24, A26	Season of birth	No association observed between genotype and season of birth	Tochigi et al. (2002)
DRD4	Season of birth	Risk association between psychosis and polymorphisms were dependent on season of birth	Chotai et al. (2003)
MTHFR (rs1801133)	Season of birth	No association between season of birth and genotype observed	Muntjewerff et al. (2011)
Residential status			
Established family history of disease	Urban living	Significant contribution to risk of developing psychosis seen in proband patients with family history of disease and living in an urban setting.	van Os et al. (2003, 2004)
Childhood trauma			
NOSAP1	Childhood abuse	No observed additive effect of risk haplotype and abuse	Husted et al. (2010)
BDNF (Val66Met)	Childhood abuse	Met carriers show positive interaction between abuse and genetics	Alemany et al. (2011)
FOXP2 (rs1456031)	Childhood abuse	Significant positive interaction between genotype and abuse, in predicting AVH in patients	McCarthy-Jones et al. (2014)
Established family history of disease	Childhood abuse	No significant association between abuse, family history and the development of psychotic disorders, in individuals reporting abuse	Fisher et al. (2014)
Stress			
COMT, BDNF, 5-HTTLPR	Chronic stress	Additive interaction between genotype and stress on reduced hippocampal volume in human subjects	Rabl et al. (2014)
COMT	Stress	COMT Val allele conveys a higher risk of psychotic outcome under stress	Stefanis et al. (2007) Simons et al. (2009)
COMT	Stress	COMT Met homozygous patients show more psychotic symptoms under stress	van Winkel et al. (2008) Collip et al. (2011)
COMT, MTHFR	Stress	Reactions to stress influenced by COMT genotype may be moderated by MTHFR genotype	Peerbooms et al. (2012)
NRG1 (rs6994992)	Stress	NRG-1 genotype influences likelihood of unusual thoughts in conflict conditions	Keri et al. (2009)
Substance abuse			
COMT	Cannabis	COMT Val carriers show higher likelihood to develop psychosis after adolescent cannabis use	Caspi et al. (2005) Henquet et al. (2006)
COMT	Cannabis	Negative findings to the above association	Costas et al. (2011) Zammit et al. (2007) Kantrowitz et al. (2009)
AKT1 (rs2494732)	Cannabis	Positive and dose dependent association between genotype, cannabis consumption and the development of psychosis	van Winkel and GROUP Investigators (2011) van Winkel et al. (2011) Di Forti et al. (2012)
CBD1 (rs12720071)	Cannabis	Positive association between cannabis use, CBD1 genotype and white matter volume in SCZ patients	Ho et al. (2011)
Established family history of disease	Cannabis	Significant association between cannabis use, family history of disease, and brain region volume	Malchow et al. (2013)
NRG1	Cannabis	NRG1 genotype and cannabis administration have an additive effect on electrophysiology results reminiscent of schizophrenia	Stadelmann et al. (2010)
Various, including DRD2, DRD4, COMT, DAT	Methamphetamine	Numerous significant associations have been found between meth use, psychotic symptoms and subject genotype	See Section 3.3.2
Obstetric complications			
Established family history of disease	Obstetric complications	Additive effect of family history and OC on CSF volume	Cannon et al. (2002a,b,c)
SCZ patient status	Neonatal hypoxia	Patients who had experienced hypoxia showed reduced hippocampal volume	Van Erp et al. (2002)
AKT1, BDNF, DTNBP1, GRM3	Obstetric complications	Linkage found between serious obstetric complications, risk of SCZ and mutations in several hypoxia related genes	Nicodemus et al. (2008)
ARVCG, FADS2	Pre-term birth	Genotype influenced white matter abnormalities in pre-term infants	Boardman et al. (2014)
GRM3	Fetal hypoxia	Severe fetal hypoxia associated with smaller hippocampal volume in SCZ patients, correlated to GRM3 genotype	Haukvik et al. (2010)

Table 2
Selected animal models of G × E in schizophrenia.

Gene	Environmental insult	Effects	References
Infection and ımmunity models			
DISC1	Prenatal poly I:C	Synergistic increases in anxiety and depressive like behaviors	Abazyan et al. (2010)
DISC1	Early postnatal poly I:C	Synergistic impairment of short term memory	Hikida et al. (2007) Ibi et al. (2010)
DISC1	Prenatal poly I:C	Synergistic increase in IL6, impaired NOR and PPI	Lipina et al. (2013)
Nurr1	Prenatal poly I:C	Synergistic impact on PPI, startle response, and latent inhibition	Vuillermot et al. (2011) Vuillermot et al. (2012)
Nurr1	*Toxopsalma gondii*	Synergistic effect on locomotor activity in open field	Eells et al. (2015)
Nrg1	Prenatal poly I:C	Several impacts: some additive, some with no combined effect	O'Leary et al. (2014)
Tap1	Influenza virus	Synergistic effects on working memory, rearing activity and anxiety	Asp et al. (2009, 2010)
Stress models			
Reelin	Maternal separation	Protective effect of mutation on social motivation	Laviola et al. (2009) Ognibene et al. (2007) Ognibene et al. (2008)
Nurr1	Social isolation, restraint stress	Synergistic impairment of PPI	Eells et al. (2006)
Sept5	Social isolation	Protective effect of mutation on anxiety like behaviors	Harper et al. (2012)
Adycap1 (PACAP)	Social isolation vs. environmental enrichment	Synergistic elevation of aggression and impact on PPI Amelioration of deficit in fear conditioning by social enrichment	Ishihama et al. (2010) Takuma et al. (2014)
DISC1	Social isolation	Synergistic increases in locomotion, immobility in FST, and PPI deficiencies	Niwa et al. (2013)
Disc1	Chronic social defeat	Opposite effects of social defeat stress on mutant vs. WT in tests of anxiety, synergistic effect on PPI and social interaction	Haque et al. (2012)
Gad67	Maternal stress	Synergistic effects on fetal cortisol and birth weight	Uchida et al. (2011) Uchida et al. (2014)
SNAP25 (*bdr*)	Maternal stress	Synergistic effects on sociability and PPI	Oliver and Davies (2009)
Nrg1	Social stress	Additive effects on locomotion, memory, sociability, and synergistic effect on brain cytokine levels	Desbonnet et al. (2012)
Nrg1	Stress in young (3–4 months) and adult (6–7 months) mice	Additive genotype–stress interaction in older mice Mutants did not display anxiety-like behavior while WT did	Chesworth et al. (2012)
Nrg1	Restraint stress during adolescence (PND 36–49)	Synergistic disruption in PPI Decreased apical dendritic length and complexity in the medial prefrontal cortex and hippocampus	Chohan et al. (2014a,b)
Rat model of *Nrg1*	Chronic stress at PND 37–44	Mutant and WT displayed less anxiety Only mutant females showed enhanced cued-fear extinction	Taylor et al. (2011, 2012, 2013)
Drug exposure models			
COMT	Cannabis	Additive decreases in size and density of dopaminergic cells	Behan et al. (2012)
COMT	Cannabis	Additive increase in startle response, PPI deficit, and decreases in anxiety	O'Tuathaigh et al. (2012)
Nrg1	Cannabis	Synergistic reduction of locomotor activity, increased anxiety, and impact on PPI	Boucher et al. (2007) Long et al. (2013)
Nrg1	Cannabidiol (CBD)	Reduced hyperlocomotion and increased social interaction in *Nrg1* improved PPI	Long et al. (2012)
DISC1	Methamphetamine	Mutation blunted response to methamphetamine, synergistic attenuated response to conditioned place preference	Pogorelov et al. (2012)
Toxin exposure models			
Reelin	Prenatal chlorpyrifos (CPF)	Protective impact of toxic exposure on USV and on stimulant response	Scattoni et al. (2009) Laviola et al. (2006) Mullen et al. (2013)
DISC1	Prenatal lead	Synergistic increases in anxiety like behaviors and in response to MK-801 administration	Abazyan et al. (2014)

present hyperactivity as a behavioral abnormality relevant to ADHD, mania, or autism, to name a few (Ridley and Baker, 1982).

The predictive validity criterion refers to the ability of a model to predict the effects of pharmacological drugs. These models are also known as pharmacological isomorphism models (Matthysse, 1986). Since pharmacological treatments of schizophrenia are symptom-oriented and are also used to treat behavioral abnormalities in other psychiatric disorders, pre-clinical models that mimic the behavioral responses to a drug provide limited insight into the molecular pathology of the disorder (Ellenbroek and Cools, 1995).

Animal models designed to achieve construct and etiological validity use epidemiologically relevant environmental and/or genetic factors to recapitulate the pathogenesis and pathophysiology of the disorder. These models are based on the notion that some behavioral abnormalities observed in humans are rooted in brain alterations that can be recapitulated in animals (Pletnikov et al., 2002).

Many current models of schizophrenia meet all the above criteria. Even so, we would like to emphasize that the main goal of a model is to address specific hypotheses or questions. Thus, there seems to be a pervasive misunderstanding of animal models

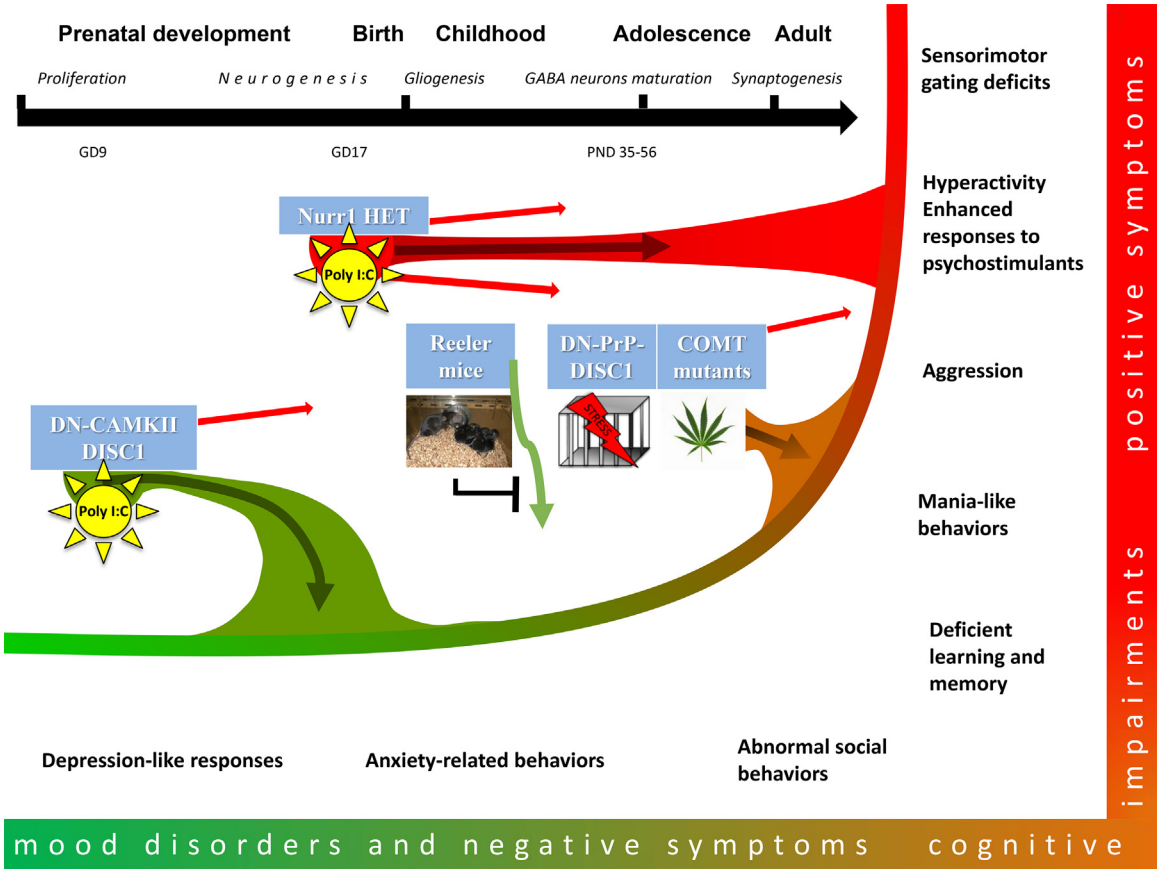

Fig. 1. Animal models of GxE in schizophrenia. The figure displays some major outcomes of G × E in different animal models. *New phenotype*: The DN-CAMKII-DISC1 × poly I:C combination demonstrates that G × E may result in a new phenotype that was not previously observed in mutant mice without an environmental challenge. For example, prenatal (GD9) exposure to maternal immune activation of mutant DISC1 mice produced the neurobehavioral alterations consistent with affective disorders (arrow in the green area) in mice that show more schizophrenia-like phenotypes without maternal immune activation (red arrow). *Stronger phenotype*: The Nurr1-HET-poly × I:C combination demonstrates the exacerbated phenotypes in mutant mice exposed to prenatal immune activation at GD17. Both genetic mutation and immune challenge are able to produce some schizophrenia-like neurobehavioral alterations (thin red arrows) but those pre-existing changes become significantly exacerbated when both factors are combined in mice. *Emerging phenotype*: The DN-PrP-DISC1 × adolescent stress or COMT x adolescent cannabis combinations produce the phenotypes that were not observed when either mutation or environmental treatment was used separately. *Protective effects of G × E*: Early maternal separation (PND 2–6) affected social behavior in WT mice but had not effects in reeler mice. The figure also depicts the main idea of the review that different combination of genetic risk factors and environmental adversities result in neurobehavioral abnormalities that represent a continuum of behavioral disorders. These behavioral alterations should not be categorized as specific diseases because phenotypic changes in mice (much like the human conditions) seem to be more accurately described by dimensional perspectives. *Abbreviations*: HET – heterozygous mice; DN – dominant negative mutant human DISC1; CAMKII or PrP – the promoters used to express DN-DISC1.

among experimental investigators and clinicians alike. It is important we avoid both overzealous promotion of any single animal model as a superior one as well as an unwarranted skepticism regarding the utility of animal models (for further discussion, see Keeler and Robbins, 2011; Fernando and Robbins, 2011). A model is valuable as far as it is able to incisively address the questions that help us understand the disease or develop a new treatment. In this context, the more animal models are used to address the diversity of pathophysiological mechanisms of a disease, the sooner we can make a real progress in this area.

Furthermore, there is a growing understanding that many psychiatric disorders share etiology and underlying pathobiology (Hall et al., 2015). Thus, the field of animal models needs to move beyond the mold of disease categories, and instead should focus on behavioral domains and dimensions. It has been argued that new preclinical models should focus on a dimensional construct and domains of psychopathology, which do not conform to the nosological categories and are consistent with increasing evidence of genetic, environmental and biological commonality between schizophrenia, bipolar disorder and other psychiatric disorders (O'Tuathaigh and Waddington, 2015). This approach is anticipated to shed more light on mental disorders as varying constellations of functional domains and will advance our knowledge of the neurobiology of basic processes that transcend diagnostic boundaries and are based on measurable phenotypes easily translatable across different species and more amenable to future biology-driven treatment (Petrinovic and Kunnecke, 2014; Hoffman, 2013; Argyropoulos et al., 2013; Mahoney and Olmstead, 2013; Cuthbert, 2014). For example, Fig. 1 depicts as different combinations of the same genetic and environmental risk factors result in varying phenotypic domains impertinent to the specific nosological category. The dimensional and RDoC framework underscores the necessity to assess the effects of genetic and/or environmental factors on domains of functions by breaking from psychiatric diagnoses and remaining agnostic toward diagnostic constrains of human psychopathology. In other words, animal models need to wean themselves from a-model-for-a-disease mold and recognize evaluating dimensions and/or endophenotypes constitutes as a way forward not only for G × E models of schizophrenia but also for the entire field of animal models of psychiatric disorders. Analyzing neurobehavioral abnormalities resulted in various G × E models within the dimensional or RDoC framework will provide a closer mechanistic connection between the model and specific domains (of the disorder) being modeled.

Prior to the RDoC concept, the approach using 'endophenotype' and 'intermediate phenotype' has been introduced (Gottesman and Gould, 2003; Kellendonk et al., 2009; Desbonnet et al., 2009; Kaffman and Krystal, 2012; Amann et al., 2010). In this context, basic research on G × E in psychotic disorders should incorporate more detailed and sophisticated examination of endophenotypes readily translatable to humans. For example, the development of cognitive tests for attention, impulsivity, working memory, and executive function has been emphasized. The perception being that these cognitive dysfunctions are the core symptoms of psychotic disorders (Powell and Miyakawa, 2006; Young and Geyer, 2015) and, as some argue, might even constitute a primary psychopathology in patients with psychotic disorders (e.g., Uhlhaas and Singer, 2015). In addition, the next generation of animal models should expand use of physiological and neural circuitry intermediate phenotypes, genome-wide gene expression and epigenetic modification profiling in specific cell types (e.g. neurons vs. astrocytes) (Kannan et al., 2013). Utilization of endophenotypic measures may not only help minimize variability in effects of G × E but also bring in new model organisms to study the molecular mechanisms of G × E across species (e.g., worms, fruit flies, zebrafish). The value of using multiple model animals is particularly evident when comparing the advantages and disadvantages mouse and rat models for G × E studies. While genetically modified mice have been, and still remain, the major workhorses among animal models, an expanding tool box of genetic manipulations in rats and the availability and reproducibility of sophisticated tests for social and cognitive behaviors are bringing back rat as a model organism for psychiatric disorders (Ellenbroek et al., 2002; Ratajczak et al., 2013).

Essentially all basic (and human) G × E studies have been performed using candidate risk factors, the majority of which have not been confirmed by the recent GWA studies (McCarroll et al., 2014; Nestler and Hyman, 2010). Although G × E studies based on rare highly penetrants mutations will remain the mainstream direction for some time, we can already see the emergence of new models that incorporate polymorphisms identified by the PGC (Quednow et al., 2014).

Further, as schizophrenia is increasingly considered a disorder of brain development, animal models with manipulation of genes involved in neurodevelopment are going to be particularly informative (Insel, 2010; Jaaro-Peled, 2009). It is important to take developmental considerations into account when interpreting environmental effects that vary across different time points (Moffitt et al., 2005; Rutter, 2008). In the past, addressing time-dependent interaction in G × E models has been achieved by changing the time when genetically modified animals are challenged with an environmental adversity. Future studies should also attempt to regulate timing of the effects of a specific mutation as exemplified by a recent study with inducible expression of mutant DISC1 in mice prenatally exposed to maternal immune activation (Abazyan et al., 2010). Similarly, more attention should be paid to time-dependent and dose-dependent effects of environmental factors. For example, maternal immune activation can produce distinct brain band behavior pathology depending on the time of prenatal exposure to poly I:C, with maternal immune activation at GD9 affecting maturation of dopamine neurons while exposure at GD17 leading to abnormalities in the development of cortical neurons (Meyer et al., 2005, 2006).

The focus of most published G × E research has been on risk factors. However, the contribution of protective factors is also important and has so far been relatively neglected, with some exceptions. Identification of genes conferring resilience to schizophrenia-related abnormalities is a new emerging field of research looking to uncover unrecognized molecular targets (Mihali et al., 2012). New models using neurodevelopmental factors of resilience are clearly needed to advance this promising research. In this context, the role for environment enrichment in ameliorating/rescuing genetically produced abnormalities has been studied in various neurodevelopmental and neurodegenerative models (Laviola et al., 2008; McOmish et al., 2008; Burrows et al., 2015) and has been recently reviewed (Nithianantharajah and Hannan, 2006; Takuma et al., 2011; Burrows et al., 2011; Pang and Hannan, 2013). Combining this type of preventive "therapy" with current G × E models would be interesting toward determining whether environmental enrichment can overcome effects caused by aversive environmental insults (e.g. psychosocial stress, infection, drug use) and offer a novel approach to treatments of the cognitive and negative symptoms that resistant to the current antipsychotics (Pratt et al., 2012; McOmish et al., 2014).

An additional step in approximating animal models to complex human condition could include combining genetic liability with several environmental factors as has been exemplified by a recent study (O'Leary et al., 2014). This line of investigation is an extension of the growing research of the role of ExE that include exposures to different environmental adversities across the lifespan with both negative and positive synergistic effects of different environmental factors (Ellenbroek and Cools, 2002; Ellenbroek, 2004; Macrì and Laviola, 2004; Harvey and Boksa, 2013; Hida et al., 2013, 2014). Meyer's lab has recently reported the potential molecular and cellular mechanisms whereby prior environmental exposure can prime the immune system of the developing brain to detrimental effects of later environmental adversity (Giovanoli et al., 2013, 2014).

We need to take animal model based research beyond studying a single pathophysiological process involved in G × E, even if the model only encompasses interaction with a single adverse event. As an example, in addition to the HPA axis, studies of stress exposure should include the immune response to stressful stimuli (Pryce and Klaus, 2013; Dantzer et al., 2008). Similarly, the role of innate and adaptive immune responses in mediating effects of illicit drugs will need to be addressed in future G × E models, going as far as to include the immune responses taking place in the intestinal tract (Severance et al., 2014).

Another issue is the under appreciation of sex-dependent effects. Many models demonstrate sex-dependent alterations, yet most G × E models focus on a single sex. Future research in G × E models should address if sex-specific abnormalities result from the effects of G × E, or the individual components, on actions of gonadal hormones or from the modulatory influence of sex hormones on the pathways involved in G × E. Advancing our knowledge of the underpinnings of sex differences in psychiatric disorders could help uncover both risk and protective factors to develop better treatments (Godar and Bortolato, 2014).

The methodologies to manipulate the mouse genome at different levels of its organization (DNA, RNA regulatory sequences) are constantly improving. Simple knockout and transgenic technologies, while remaining the workhorse of mouse genetics, produce artificial systems inconsistent with the molecular pathology of schizophrenia. New models with mutations in regulatory elements of candidate genes, which show subtler, and temporally specific expression changes, or human genetic variants knock-in models, both better reflect the complex genetic and molecular mechanisms of schizophrenia (Chen et al., 2006; Papaleo et al., 2012). Therefore, time-dependent, circuitry- or cell-specific manipulations to target mRNA and/or proteins should be utilized where available.

There is growing appreciation that combining multiple genetic mutations or several environmental factors in a single model could be more informative. In addition to conventional breeding approaches, newer technologies include plasmid-based cell-type-specific and inducible expression systems using in utero

gene transfer by targeting multiple genes (Taniguchi et al., 2012). A complementary methodology is to suppress the expression of target genes using RNA interference (RNAi) knockdown technology (Mello and Conte, 2004). Several susceptibility genes can be knocked down simultaneously in mice carrying multiple siRNA expression transgenes.

Most studies have focused on neuronal functions of susceptibility genes. However, these genes are also expressed by glial cells (Iijima et al., 2009). Given, growing interest in the role for glia cells in mediating the effects of stress and microbial pathogens, G × E models with cell-specific perturbation of candidate genes are also needed. A recent study has provided the first evidence for the potential role of DISC1 in astrocytes, connecting DISC1 and serine racemase in modulating NMDA receptor functions (Ma et al., 2013). Our understanding of neuron-astrocyte interaction in health and disease is unlikely to be facilitated without tools that allow us to monitor and manipulate astrocytes in behaving animals. Recent studies utilizing optogenetics and two-photon microscopy in combination with behavioral tests have demonstrated the possibility of developing and characterizing such models (Sasaki et al., 2012; Paukert et al., 2014).

In conclusion, G × E animal models have already begun to provide new insights into the etiological complexity and heterogeneity of schizophrenia. We believe G × E animal models will continue to be a crucial tool to advance our knowledge about this debilitating disorder. The challenge ahead for G × E animal models is to provide mechanistic insights in how genetic and environmental factors interact, with the hope that identifying the convergent molecular pathways will lead to uncovering new therapeutic targets and/or disease biomarkers.

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