INTRODUCTION

Awareness is increasing that the burden created by psychiatric disorders is enormous, as is the amount of research conducted on the causes of mental illnesses (Murray et al., 2012). With 0.5–0.7% of the human population affected by schizophrenia (Saha, Chant, Welham, & McGrath, 2005), it represents a major public health concern, having an overall disability burden exceeding that of many infectious diseases (Murray et al., 2012). Despite its enormous impact and the work being done to understand it, the disease is still defined by many variable symptoms without a single unifying definition of presentation. Put as simply as it is possible to, schizophrenia is a debilitating psychiatric disorder characterized by positive (e.g., hallucinations and delusion), negative (e.g., social withdrawal and flat affect), and cognitive impairment. These abnormalities usually lead to a lifelong disability, reduced socioeconomic status, and increased risk for suicide among patients (Goldberg et al., 2011).

Heterogeneous clinical manifestations and symptoms of schizophrenia overlap with those of other psychotic disorders (i.e., bipolar and substance-induced psychotic disorders). This continuity of presentation with other diseases, and also growing genetic evidence, has caused many researchers to question the very concept of schizophrenia as a disorder (Berrios, Luque, & Villagran-Moreno, 2003). This uncertainty has also led to the development of diagnosis category-independent perspectives for psychotic disorders, including dimensional approach and research domain criteria matrix. van Os and Kapur (2009) propose to group symptoms of psychotic disorders 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. Also reflecting this sea change in the view of schizophrenia disease, a review of schizophrenia by a group of prominent psychiatrists has led to the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders now including dimensional assessments (Heckers et al., 2013).

Meta-analysis of twin studies has estimated the heritability for schizophrenia at approximately 80%, and the impact of environmental influences on risk to account for a value near 11% (Sullivan, Daly, & O’Donovan, 2012; Sullivan, Kendler, & Neale, 2003). The psychiatric research field is approaching consensus that gene–environment interaction (GEI) plays a considerable role in the pathogenesis of the disorder (van Os & Kapur, 2009; Uher, 2014). The chapter overviews existing animal models of GEI related to schizophrenia. In doing so, we
suggest a modification in research approach. Given the complexity of human disease manifestation and etiology, the existing research highlights the need in focusing on modeling a specific disease as an etiologically and pathobiologically separate category (Nestler & Hyman, 2010). Instead, consistent with the main theme of the book (please, also see the chapter by John Waddington), we suggest that a dimensional approach will better facilitate mechanistic studies to understand GEI in schizophrenia and other psychotic disorders.

GENES AND ENVIRONMENT IN SCHIZOPHRENIA

The greatest progress in understanding the genetics of schizophrenia has come from the large sample-sized genome-wide-association studies (GWAS). Psychiatric Genomics Consortium, established in 2007, is made up of more than 500 investigators from 25 countries (Sullivan, 2010). The latest Psychiatric Genomics Consortium paper describes the genotyping data of 36,989 cases and 113,075 controls. With this sample size, 108 loci contributing to risk of schizophrenia were identified including 25 replicating and 83 newly described risk markers. More than 70% of discovered loci were located in regions encoding proteins involved in dopaminergic and glutamatergic neurotransmission, calcium signaling, synaptic plasticity, potassium channels, and neurodevelopment (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Single nucleotide polymorphisms in the extended major histocompatibility complex region on chromosome 6 were significantly associated with schizophrenia, suggesting etiological relevance of immune responses and inflammatory pathways (Shi et al., 2009; Sullivan et al., 2012). Genomic structural alterations also play an important role in etiology of schizophrenia (Walsh et al., 2008; the Chapter 15B by N. Hiroi). Various mutations affecting single genes were found in several families exhibiting large phenotypic abnormalities (Goate et al., 1991; Klein & Westenberger, 2012; Rogan et al., 1995).

There are many environmental insults that have been found to be associated with schizophrenia. Among them are in utero exposure to infection, diet, perinatal complications, maternal malnutrition, stressful events during pregnancy, and early postnatal development as well as substance abuse (Brown, 2011; Meyer & Feldon, 2010). It is important to note, however, that the various environmental risk factors are suggested to lead to development of schizophrenia by engaging genetic liability for the disorder, which in itself is not enough to result in any clinical phenotype (van Os & Kapur, 2009; Rethelyi, Benkovits, & Bitter, 2013; Uher, 2014).

GEI includes a genetic control of responses to protective or adverse environment, and often a dependency of genetic effects on an environment (i.e., genetic effects can be stronger in one environment than in the other) (Rutter et al., 2006). In some cases, both GEI and rGE can be involved. As an example, polymorphisms of one of the genes for the alcohol dehydrogenase enzyme family, the ADH1B, contribute to fetal alcohol spectrum disorders (FASD). Whereas ADH1B*1 has been suggested to be a risk factor for FASD, ADH1B*2 and ADH1B*3 have been shown to reduce the risk for FASD. Because these
gene variants have differential impacts on susceptibility to the effect of alcohol, they may refer to GEI. At the same time, the association between alcohol exposure in utero and FASD may refer to a passive rGE since mothers who carried the ADH1B*1 allele are identified to be at higher risk for greater alcohol consumption than mothers who carried the ADH1B*2 or 3. This example suggests that investigators who measure genes and environments should be observing for both rGE and GEI (Edenberg & Foroud, 2013).

Recent epidemiological studies have shed light on the underpinnings of GEI relevant to schizophrenia and related psychotic disorders (Modinos et al., 2013; van Winkel, van Beveren, Simons, & Genetic Risk and Outcome of Psychosis (GROUP) Investigators, 2011). Even if the available GEI results are limited, they have allowed for developing animal models to determine the molecular and neurobiological mechanisms, whereby environmental and genetic risk factors interact to lead to schizophrenia (Iyegbe, Campbell, Butler, Aajakina, & Sham, 2014).

ANIMAL MODELS OF GEI RELEVANT TO SCHIZOPHRENIA

The main goal of animal models of GEI is to provide mechanistic insights into how genetic and environmental factors interact with each other to explain the heterogeneity of clinical manifestations and symptoms of schizophrenia (Ayhan et al., 2009; Hida et al., 2013; Kannan, Sawa, & Pletnikov, 2013; Rethelyi et al., 2013; van Winkel et al., 2011). The main environmental risk factors applied to GEI animal models can be largely separated into four groups: immune dysfunction, stress, substance abuse, and environmental toxins.

Models of Immune Activation

Several lines of evidence suggest that prenatal and early childhood infections increase the risk of schizophrenia. In particular, maternal infection and in utero exposure to influenza as well as toxoplasma have been shown to increase the risk of schizophrenia in offspring (Brown, 2011). One of the most popular approaches to simulate prenatal infection is maternal immune activation (MIA) using viral or bacterial-like immune activating agents (Meyer & Feldon, 2012; and Chapter 12A by Malkova et al.). This approach is widely used with mice carrying genetic variants of the candidate genes.

Interaction with DISC1

The first studies of GEI applying MIA to a genetic model were done using mice carrying human mutations of Disrupted-In-Schizophrenia (DISC1), a rare genetic factor associated with major psychiatric disorders (Porteous et al., 2011). DISC1 has been shown to regulate major neuronal functions, including neural proliferation, migration, dendritic arborization, spine formation, and the maintenance of synapses (Brandon & Sawa, 2011; Wen et al., 2014). Recently, the important role of DISC1 in regulation of mitochondrial functions, oligodendrocyte differentiation, and astrocyte functioning has also been demonstrated (Eykelenboom et al., 2012; Kim et al., 2012; Ma et al., 2013; Park et al., 2010; Wood, Bonath, Kumar, Ross, & Cunliffe, 2009). Our group generated a transgenic model of inducible expression of mutant human DISC1, a putative product of the translocation (Pletnikov et al., 2008). 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 the Morris water maze in females.

To assess the interaction of DISC1 and MIA, mutant DISC1 mice were prenatally exposed to polyinosine-polycytidylic (poly I:C) treatment of pregnant dams (Abazyan et al., 2010). Injection of pregnant mice with poly I:C at gestational day (GD) 9 resulted in the altered pattern of secreted cytokines in the mutant DISC1 fetal brains. In addition, a prenatal exposure to poly I:C increased anxiety-like and depressive-like behaviors and decreased sociability in adult mice carrying DISC1 mutation. These findings have been correlated with the morphometric analysis of amygdala and peri-ventricular gray matter, brain regions involved in the circuitries of fear and anxiety responses. The volumes of these regions were significantly decreased in mutant mice treated with poly I:C. In addition, MIA led to altered functioning of the hypothalamus-pituitary-adrenal axis by blunting the corticosterone response of DISC1 mice to restraint stress. Importantly, the expression of mutant DISC1 was necessary during the entire period of prenatal and postnatal development to induce neurobehavioral alterations following immune challenge (Abazyan et al., 2010).

Another group evaluated the effect of poly I:C exposure during early postnatal development using the mouse model constitutively expressing mutant DISC1 (Hikida et al., 2007). Poly I:C injection for 5 consecutive days from postnatal day (PND) 2 resulted in the impaired short-term memory in adulthood in both control and mutant mice. Yet, only in mutant DISC1 mice did it also produce impaired fear memory, increased locomotor activity, decreased social interaction, and increased aggressive behaviors. Moreover, immune response activated by poly I:C treatment in mutant DISC1 mice resulted in the decreased number of parvalbumin positive cells in the medial prefrontal cortex (PFC) and the increased number of BrdU-positive cells (an indicator of neurogenesis) in the granular cell layer of the dentate gyrus of the mouse hippocampus. This study has
demonstrated that some schizophrenia-resembling abnormalities (e.g., reduced parvalbumin reactivity) can be precipitated by an early postnatal immune challenge in DISC1 mice (Ibi et al., 2010).

Interaction of poly I:C exposure with expression of mutant DISC1 genes were also investigated using Disc1-L100P and Disc1-Q31L mutant mice carrying Q31L and L100P point mutations in the second exon of the Disc1 gene, respectively (Clapcote et al., 2007). Intact Q31L mutant mice demonstrate increased immobility in forced swim test (FST), decreased sociability and social novelty, and reduced sucrose consumption, consistent with depressive-like phenotypes. L100P mutant mice show the increased locomotor activity, decreased prepulse inhibition (PPI) of the acoustic startle and latent inhibition (LI) and a poor memory assessed in T-maze. Both Q31L and L100P heterozygous animals were challenged with poly I:C MIA at GD 9. MIA reduced sociability, worsened PPI deficit, and impaired novel object recognition in all tested animals. However, compared with wild-type (WT) animals and Disc1-Q31L, Disc1-L100P mutants were more sensitive to the effects of MIA, consistent with the concept of GEI. MIA also resulted in increased IL-6 expression in the fetal brains, with a strongest effect being observed in L100P mice. Notably, anti-interleukin-6 (IL-6) treatment reversed the poly I:C effects on PPI and LI in mutant mice, supporting the previous findings that IL-6 mediates adverse effects of MIA.

Interaction with Neuregulin-1

Neuregulin-1 (NRG1) is a protein that plays the important role in synaptic plasticity and neuroinflammation (Li, Woo, Mei, & Malinow, 2007). In addition, it has been shown that mutations in the NGB1 gene are associated with schizophrenia. NRG1 interacts with IL-1β and increases the activation of pro-inflammatory cytokines such as IL-6, IL-8, and TNF-α in patients with schizophrenia (Marballi et al., 2010). O’Leary et al. (2014) employed a complex design of cross-fostering to assess multiple effects of GEI, including dams’ behaviors following an adverse environmental exposure during pregnancy. The study evaluated the schizophrenia-related interactions between MIA and NRG1. Several behavioral abnormalities were found depending on the combinations of NRG1, prenatal insult, and cross-fostering. The authors propose that numerous interactions of individual genes and different environmental factors are to be analyzed and recreated in future animal models.

Modeling of Stress

Multiple observations lead to an increasing appreciation that stress is a major environmental risk factor for psychiatric illness (Dvir, Denietolis, & Frazier, 2013; Fine, Zhang, & Stevens, 2014; van Winkel et al., 2008). To modulate stressful events in animals several different approaches can be used. The most popular ones are prenatal stress (Hillerer, Neumann, & Slattery, 2012; Markham & Koenig, 2011), maternal separation (Bocca et al., 2007), or social defeat paradigm (Willner et al., 1984; Nestler & Hyman, 2010). Several recent reviews have described the effects of the prenatal and postnatal stresses on the activity of the hypothalamus-pituitary-adrenal axis and resultant behavioral phenotypes, and readers are directed to these reviews (Koenig, 2006; Weinstock, 2005; also, please see the Chapter 12C by F. Cirulli).

Interaction with Reelin

Reelin is a large extracellular matrix glycoprotein involved in neuronal migration in the developing brain through control of cell–cell interactions
(Rogers & Weeber, 2008). The lack of reelin expression in mutant reeler mice leads to defects in neuronal position and dendrite development. Reelin messenger RNA (mRNA) and protein levels have been found to decrease in brain (Impagnatiello et al., 1998) and blood (Fatemi, Kroll, & Stary, 2001) of schizophrenia patients. The decreased neuronal levels of reelin were accompanied with increased activity of D-N-methyltransferase, suggesting that hypermethylation in the reelin promoter might be responsible for decreased reelin expression (Eastwood & Harrison, 2003; Grayson et al., 2005; Ruzicka et al., 2007). Yet, while a reduced reelin level has been confirmed by many studies (Fatemi, Earle, & McMenomy, 2000; Guidotti et al., 2000), some works failed to reproduce these results (Tochigi et al., 2008). Therefore, this suggests that additional factors can be implicated in the reelin-related pathophysiology of schizophrenia.

Early maternal separation was associated with reduced reelin, brain-derived neurotrophic factor (BDNF), and glia-derived neurotrophic factor levels over the developing period in WT mice (Ognibene et al., 2008; Zhang, Qin, & Zhao, 2013). Interactions between early maternal separation and reeler expression have been studied using a protocol of 5h of daily maternal separation applied from PND 2–6 (Laviola, Adriani, Gaudino, Marino, & Keller, 2006). The social motivation was assessed by the homing test paradigm conducted on PND 9. During this test the locomotor activity directed by motivation to find the nest was measured. However, whereas maternal separation applied to WT mice significantly reduced social motivation, homzygous and heterozygous reeler mice were found unaffected (Ognibene, Adriani, Macri, & Laviola, 2007). Also, the decreased body weight found in WT mice after maternal separation was not detected in heterozygous reeler mice. Furthermore, maternal separation resulted in a smaller decline in expression of BDNF and glia-derived neurotrophic factor but enhanced stimulating effects of antipsychotic treatment on BDNF levels. Moreover, reelin level was upregulated in 3-month-old male mice as a result of maternal separation. These observations allowed the authors to hypothesize that the “beneficial” effects of maternal separation in reeler mice may result from a compensation of neural plasticity defects, most probably by the activation of hormonal steroid pathways.

**Interaction with Nurr1**

Another approach to recapitulate aspects of childhood trauma includes social isolation (SI) during adolescence. SI between PND 19–21 of heterozygous Nurr1 mice has been shown to result in impaired PPI when assessed 12 weeks after the cessation of isolation in adult mice and was accompanied by decreased levels of DA and dihydroxyphenylacetic acid in the PFC in mutants but not in WT animals (Eells, Misler, & Nikodem, 2006). However, corticosterone levels measured in mutants and controls before and after isolation did not reveal any group differences, suggesting that SI does not affect stress reactivity in mutant mice (Eells et al., 2006).

**Interaction with SEPT5**

The effects of SI were also studies in a mouse model of the SEPTIN5 (SEPT5) gene. The gene is located within 22q11 region, and therefore it has long been considered as a possible risk factor for schizophrenia (Harper et al., 2012). SEPT5 is expressed in the brain both during neurodevelopment and adulthood (Asada et al., 2010) and involved in vesicular exocytosis by binding to syntaxin in presynaptic soluble N-ethylmaleimide-sensitive factor attachment receptor complexes (Beites, Campbell, & Trimble, 2005). SEPT5 KO mice exhibit decreased social interaction, increased PPI, and spent more time in the open arms of the elevated plus maze. 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). Moreover, virally guided overexpression of SEPT5 in the hippocampus or amygdala enhanced social interaction in C57BL/6j mice. In addition, it has been shown that individually postweaning housing leads to the elevated SEPT5 level in the amygdala and increased active affiliated social interaction in comparison to group-housed animals. Compared with group-housed mutants, single-housed mice 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 with group housed mutants, consistent with reduced anxiety levels. This study is another example when seemingly adverse environmental effects may interact with a genetic mutation to ameliorate the negative effects of either one presented separately (Harper et al., 2012).

**Interaction with Pituitary Adenylate Cyclase-Activating Polypeptide**

Pituitary adenylate cyclase-activating polypeptide (PACAP) is a neuropeptide that displays structural similarity to vasoactive intestinal peptide and a member of the secretin/glucagon/vasoactive intestinal peptide family. PACAP is crucial for the regulation of circadian rhythms, axonal maturation, axonal integrity, and cellular stress responses (Waschek, 2013). PACAP is encoded by the ADYCAP1 gene located in locus associated with schizophrenia to 18p11.32 (Farone et al., 2005; Mukherjee et al., 2006; Schwab et al., 1998). In addition, ADYCAP1 variants were associated with schizophrenia, deficits in verbal memory, and hippocampal volume (Hashimoto et al., 2007; Koga et al., 2010). Moreover, PACAP directly interacts
with DISC1-Binding Zinc-finger protein resulting in increased DISC1 expression and reduction in neurite outgrowth, both of which are suggested as factors potentially relevant to schizophrenia (Hattori et al., 2007).

In a study addressing whether stress can modulate the phenotype of mice lacking the Adycap1 gene, animals were subjected to two different rearing conditions, namely a short-term SI at PND 28 or environmental enrichment (EE) starting at PND 28 or 56. SI applied to Adcyap1−/− mice resulted in increased locomotor activity, decreased latency to attack, and increased attacking time in social interaction tests, suggesting elevated aggression. In addition, SI further led to decreased PPI in mutants. On the contrary, EE started from PND 28 but not from PND 56 decreased hyperactivity; increased time spent in social interaction tests and decreased duration of immobility in FST. Importantly, this applied earlier EE worsened the results of PPI in Adcyap1−/− mice (Ishihama et al., 2010), suggesting that outcome of EE × PACAP is time-dependent and cannot be explain by “rescue” effects of positive environment.

Thus, ameliorative effects of cannot be generalized to all behavioral changes, with some, in fact, possibly being adverse (Burrows, McOmish, & Hannan, 2011; Takuma, Ago, & Matsuda, 2011). Still, exposing mutants to may shed some light on this “preventive” therapy and might point to treatments of the cognitive and negative symptoms that resistant to the current antipsychotics (Pratt, Winchester, Dawson, & Morris, 2012).

Interaction with DISC1

Recently, a dominant negative mouse model with expression of mutant DISC1 under the PrP promoter was used to study stress effect on animals expressing DISC1 mutation. Mutant and control were exposed to 3-week isolation from 5 to 8 weeks of age. It was found that only mutants exposed to SI displayed increased locomotor activity, deficient PPI, and increased immobility in FST, suggesting GxE effects. These effects were associated with decreased extracellular levels of DA and tyrosine hydroxylase expression, and increased D2R expression in the frontal cortex and increased DA levels in the nucleus accumbens, the main forebrain targets of DA projections of the ventral tegmental area. SI applied to these mice resulted in increased corticosterone level, hypomethylation of the tyrosine hydroxylase promoter, and selectively reduced tyrosine hydroxylase expression in the mesocortical pathway. Treatment with glucocorticoid receptor antagonist, mifepristone, rescued the SI-induced behavioral and biochemical abnormalities (Niwa et al., 2013).

The GEI effects of chronic social defeat (CSD) were evaluated in mice carrying Q31L or L100P Disc1 mutations. CSD applied at PND 50 for 20 days resulted in increased time spent in open arms of the elevated plus maze in Q31L mice. However, this time was significantly decreased in L100P mice after CSD. Also, CSD led to diminished PPI and enhanced sociability and social novelty in L100P mutants (Haque, Lipina, Roder, & Wong, 2012).

Interaction with Glutamic Acid Decarboxylase

Glutamic acid decarboxylase (GAD) is an enzyme responsible for conversion of glutamate to gamma-aminobutyric acid (GABA). Decreased expression of GAD, specifically the GAD67 isoform, has been found in Parvalbumin-positive interneurons in the PFC of schizophrenia patients (Akbarian et al., 1995; Beneyto, Morris, Rovensky, & Lewis, 2012; Curley et al., 2011; Hashimoto et al., 2003; Kimoto, Bazmi, & Lewis, 2014; Volk, Austin, Pierri, Sampson, & Lewis, 2000; Volk et al., 2012). Reduced GAD67 expression has also been accompanied with increased levels of DNA methyltransferases, which silence transcription by methylation of the promoter region (Veldic, Guidotti, Maloku, Davis, & Costa, 2005). Recent data suggest that methylation is a dynamic process that can be activated in response to stressful environmental factors and lead to abnormal development and functions of GABAergic neurons (Fine et al., 2014). Prenatal stress has been used in an animal model that was designed as knock-in mice expressing green fluorescence protein under GAD67 promoter to label GAD67-positive interneurons (Tamamaki et al., 2003). Therefore, heterozygous mice have reduced GAD67 expression and can be considered as a knock-down GAD67 model (Tamamaki et al., 2003). Restraint-and-light stress at GD17 increased maternal cortisol levels in both WT and knock-down GAD67 mothers, with mutant having a greater increase. Maternal stress resulted in decreased fetal body weight, which was much lower in the mutant fetuses. Moreover, fetal cortisol levels in mutants were much higher (Uchida, Oki, Yanagawa, & Fukuda, 2011). Restraint-light stress during GD15–17.5 was associated with the decreased number of parvalbumin-positive interneurons in the PFC, somatosensory cortex, and hippocampus of mutant offspring only (Uchida, Furukawa, Iwata, Yanagawa, & Fukuda, 2014).

Interaction with Synaptosomal-Associated Protein-25

Synaptosomal-associated protein-25 (SNAP25) is a presynaptic protein that takes part in vesicular exocytosis (Chen & Scheller, 2001), neurite outgrowth (Wu et al., 2011), and long-term potentiation (Jurado et al., 2013). Evaluation of synaptic proteins in the postmortem samples revealed decreased SNAP25 levels in the frontal and temporal lobes (Karson et al., 1999; Thompson, Sower, & Perrone-Bizzozero, 1998), and also in the entorhinal
cortex (Young et al., 1998), hippocampus (Fatemi, Earle, Stary, Lee, & Sedgewick, 2001; Thompson, Egbufoama, & Vawter, 2003), and cerebellum (Mukaeova-Ladinska, Hurt, Honer, Harrington, & Wischik, 2002) of schizophrenia patients. Additional evidence for the role of SNAP25 came from relatively small-scale genetic epidemiologic studies, some of which reported positive associations with SNAP25 variants and schizophrenia (Carroll, Kendall, O’Donovan, Owen, & Williams, 2009; Lochman, Balcar, Stastny, & Sery, 2013), but negative studies also exist (Dai et al., 2014; Kawashima et al., 2008). I67T point mutation in SNAP25 results in an increased binding affinity within the core SNARE complex, preventing the normal recycling of synaptic vesicles. Mice carrying this dominant mutation were named blind-drunk (Bdr) because of its distinctive ataxic gait (Jeans et al., 2007). Bdr mice displayed 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 have been observed in these mice (Oliver et al., 2012). Stressful treatment of Bdr and control mice resulted in reduced PPI that could be improved with antipsychotics (Oliver & Davies, 2009). However, only Bdr mice subjected to prenatal stress showed decreased time spent with another mouse (as a sociability index) and decreased time spent with a novel stranger mouse (as a social novelty index).

Interaction with NRG1

NRG-1 mutations are associated with impairments in glutamatergic, dopaminergic, and GABAergic neurotransmission (Li et al., 2007; Newell, Karl, & Huang, 2013). Nrg1 is necessary for the establishment of excitatory synapses in GABAergic interneurons and for the development of a balanced excitatory/inhibitory tone in the brain (Ting et al., 2011). 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., 2004; Stefansson et al., 2003; Thiselton et al., 2004; Williams et al., 2003). Several postmortem studies indicated increased NRG1 signaling in schizophrenic patients (Chong et al., 2008; Hahn et al., 2006; Hashimoto et al., 2004). Upregulation of NRG1 signaling leads to increased GABAergic inhibition of glutamatergic pyramidal neurons, resulting in a hypo-glutamatergic state (Deng, Pan, Engel, & Huang, 2013; Mei & Nave, 2014; Mei & Xiong, 2008). Also, NRG1 polymorphism interacts with the psychosocial stress modifying reactivity to expressed emotions in schizophrenia patients (Keri et al., 2009). Therefore, several research teams have investigated the response of Nrg1 rodent models to stress. A NRG1 knock-down model carrying mutation in the transmembrane domain has demonstrated increased spontaneous activity, an anxiolytic-like phenotype, and PPI deficiency (Golub, Germann, & Lloyd, 2004). CSD was applied to these mutants starting on PND35. When evaluated at adulthood, CSD in Nrg1 mutant mice 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. Analyses of selected immunological variables were carried out and revealed that CSD in mutants differentially increased the levels of basal cytokines and caused variable changes in IL-1β and TNF-α levels in different brain regions (Desbonnet et al., 2012).

Modeling Substance Abuse

Cannabis

Long-term and high-dose cannabis use during adolescence significantly increase the risk for schizophrenia development in adulthood (Andreasson, Allebeck, Engstrom, & Rydberg, 1987;Arseneault et al., 2002; Fergusson, Horwood, & Ridder, 2005; van Os et al., 2002). Also, epidemiologic studies indicate that early use of cannabis is associated with an earlier onset of schizophrenic symptoms (Barnes, Mutsatsa, Hutton, Watt, & Joyce, 2006). Still, the role of cannabis use in schizophrenia remains poorly understood. One suggestion is that heavy cannabis usage during adolescence may have particularly harmful effects on cognition and the development of psychoses in genetically vulnerable individuals (Murray et al., 2012). Clinical and preclinical studies have suggested that genes encoding to proteins involved in DA signaling can contribute to the cannabis–psychosis association (O’Tuathaigh et al., 2012).

Interaction with COMT

COMT is an enzyme involved in degradation of DA, the role of which has been extensively evaluated as it relates to the pathogenesis of schizophrenia. Also, increased risk of psychosis was associated with deletion of 22q11, where COMT gene is located (Gothelf et al., 2014; Karayiorgou et al., 1998; Murphy, Jones, & Owen, 1999; Paterlini et al., 2005). In addition, the COMT Val-158Met polymorphism was demonstrated to moderate the effects of cannabis use on adult psychosis (Heim, Coyne, Kamboh, Ryan, & Jennings, 2013; Mueller, Makeig, Stemmler, Hennig, & Wacker, 2011; Nixon et al., 2011; Uçok, Ozturk, Duman, & Saruhan-Direskeneli, 2010; Wirgenes et al., 2010).

COMT-deficient mice have been available for close to two decades, allowing for several interesting lines of inquiry with this model (Gogos et al., 1998). Homozygous mice have no COMT activity, accompanied with
increased levels of dihydroxyphenylacetic acid and homovanillic acid, but no changes in striatal, cortical, or hypothalamic content of DA or noradrenaline (Huotari et al., 2002). Heterozygous mutants displayed increased sitting and chewing, and reduced “free” rearing (Babovic et al., 2007). To evaluate possible effects of GEI between cannabis and COMT variants, COMT-deficient mice were exposed to chronic adolescent tetrahydrocannabinol (THC) treatment, an active ingredient of cannabis, at PND 32–52. Adolescent THC treatment led to increased exploration, impairment in spatial working memory, and a stronger antianxiety effect in COMT KO mice compared with WT. The study demonstrated interaction between genes and adverse environmental exposures over adolescence a particular stage of development in the expression of the psychosis phenotype (O’Tuathaigh et al., 2010). A follow-up study also showed that adolescent THC exposure resulted in decreased density and soma size of dopaminergic neurons in the ventral tegmental area (Behan et al., 2012). A related work from the same group assessed the effects of treatment with the cannabinoid receptor agonist, WIN 55212, of COMT mutants at PND 32–52. This treatment, assessed 21 days later, led to increase of the startle response, decrease of PPI, and increase of the time spent in light area in light/dark test in mutant mice. Notably, the COMT inhibitor, tolcapone, reversed all these effects, suggesting that at least some of the behavioral effects in COMT-deficient mice are mediated by disturbances of DA metabolism (O’Tuathaigh et al., 2012).

Interaction with NRG1

The clinical importance of NRG1 cannabis interaction has recently been shown by a genetic study in African-Americans, which found that NRG1 is major candidate for the development of cannabis dependence (Han et al., 2012). This observation is in line with an early experimental study demonstrating that NRG1-deficient mice exposed to THC displayed no differences in the appearance but exhibit increased spontaneous activity and deficient PPI (Golub et al., 2004).

Analyses of Nrg1 × cannabis interactions in transmembrane domain Nrg1-mutant mice (Nrg1 KD model) suggest that Nrg1 increases the susceptibility to the neurobehavioural effects of cannabis (Boucher et al., 2007). In this study, 6–7-month-old WT, Nrg1 KO, and KD animals were tested for acute THC treatment effect. Native Nrg1 KD mice spent more time in the light compartment in light–dark and in open arms in elevated-plus maze tests and displayed hyperactivity. Only in these mice but not in controls, THC treatment led to reduced locomotor activity, decreased time spent in open arms, and decreased time spent in light area and changed PPI. Similar results were received when Nrg1 mice were treated with THC from PND 21–32 and a comprehensive evaluation was carried out at adulthood. THC administration resulted in a decreased hyperactive phenotype in mutant mice. Furthermore, THC chronic treatment led to sniffing reduction (an index of social interaction). The effects of chronic THC administration can be at least in part explained by increased CB1R binding and affected 5HT2A and NMDA receptor binding in Nrg1 mutants (Long et al., 2013).

Methamphetamine

Besides cannabis, methamphetamine (METH) was also implicated in the pathophysiology of schizophrenia in some populations. Chronic METH abuse commonly leads to psychoses similar to those of schizophrenia (Bramness et al., 2012; Callaghan et al., 2012; Hsieh et al., 2014; Li et al., 2014). The first evidence of METH-induced psychosis came from Japan after the 1950s epidemic of METH use and was described as a long-lasting psychotic syndrome following METH-associated brain damage (Sato, 1992). The second and third epidemic in Japan followed at 1980s and 1990s, respectively, and the characteristics of the syndrome was defined as progressive impairment in mental and cognitive status with repeated use, vulnerability to relapse of psychotic symptoms, and a long duration for this vulnerability (Ujike & Sato, 2004). Similar to cannabis use, GEI may play a role in the genesis of METH-associated psychosis. A recent study has revealed that the risk alleles for METH-induced psychosis were enriched in schizophrenia GWAS dataset (Ikeda et al., 2013).

Interaction with DISC1

Our laboratory has evaluated putative effects of chronic METH administration in mutant DISC1 mice. To mimic a pattern of human METH abuse, a nontoxic, gradually escalating dose regimen was used. Specifically, METH doses were gradually increased over a 2-week period. Mutant DISC1 mice exhibited reduced 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 to moderate their contribution to schizophrenia (Pogorelov et al., 2012).

Environmental Toxins Models

Organophosphates

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, organophosphates were used to model abnormal neurodevelopment as prenatal organophosphates exposure was linked to neurocognitive impairment (Whyatt & Barr, 2001.)

Previously it was shown that chlorpyrifos (CPF), an organophosphate pesticide, might induce behavioral disturbances after intrauterine exposure, consistent with epidemiological (Whyatt & Barr, 2001) and animal data (Levin et al., 2002). It was hypothesized that a deficiency in reelin may ameliorate the abnormal behavioral rose by CPF insults. Pregnant heterozygous reelin females were exposed to CPF to assess the effects prenatal treatment on neurobehavioral development of the offspring. Decreased ultrasonic vocalization as a measure of communication in mice was tested at PND7 and found increased in reeler mice up to WT levels after CPF treatment (Scattoni, Crawley, & Ricceri, 2009). 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, Khaleeva, Hoffman, Ghiani, & Carpenter, 2013). These findings may be relevant to cholinergic abnormalities in autism and schizophrenia and demonstrate how adverse effects of environmental toxins could become paradoxical when combined with genetic variants.

**Lead**

Exposure to lead (Pb^{2+}) during prenatal and early postnatal development was recently also suggested as potential environmental risk of schizophrenia (citations). 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 NMDA receptors (Guilarte, 2009).

To experimentally test this hypothesis, we investigated the effects of prenatal exposure to Pb^{2+} in mutant DISC1 mice (Abazyan et al., 2014; Guilarte, 2009). The experimental groups of mice were fed with moderate levels of Pb^{2+} throughout their lifetime, whereas the control group received regular 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, Pb^{2+} exposure and mutant DISC1 additively increased locomotor activity induced by the NMDA receptors antagonist, MK-801. Because Pb^{2+} plays a role in vesicular exocytosis and high doses alters the structure and formation of NMDA-containing synapses (Neal, Stansfield, Worley, Thompson, & Guilarte, 2010; Neal, Worley, & Guilarte, 2011), we tried to rescue the effects of Pb^{2+} by administering an NMDA receptor coagonist, d-serine. d-serine is an allosteric modulator of NMDA receptors and has been used in translational studies as well as in clinical trials (Kantrowitz et al., 2010; Labrie & Roder, 2010; Yang & Svensson, 2008). DISC1 binds serine racemase, the enzyme producing d-serine and mutant DISC1 decreases d-serine production by altering the binding properties of serine racemase (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.

**SUMMARY**

Recent advances in genetics and epidemiology have provided the foundation for the development of GEI animal models relevant to schizophrenia. The existing animal preparations model the complex interactions between different factors implicated in the disorder as summarized in Table 1.

In reviewing the models published for the past 5–6 years, one can identify the main features common among many models. Although many investigators seem to expect detecting synergistic effects of a genetic mutation and an environmental adversity, there have been described different results of GEI as well. It is not uncommon to observe so-called “protective” effects in some GEI models or neurobehavioral changes that were not previously seen in any of experimental groups. These diverse outcomes of GEI are consistent with the notion of the shared etiology and underlying pathobiology of several psychiatric disorders (Hall, Trent, Thomas, O'Donovan, & Owen, 2015; Insel, 2010). This book is a first compilation of the chapters to argue that animal models should stop mimicking a disease as a category and instead focus on recapitulating and assessing dimensions and endophenotypes as a way of advancing the field of GEI (see the Chapter 3 by J. Waddington).

**FUTURE PROSPECTS**

Recent progress in psychiatric genetics and epidemiology has facilitated the development of animal models of GEI relevant to schizophrenia. Although these models have provided some important insights, many caveats of recent preparations need to be addressed in the future studies.

To overcome these roadblocks for the clinical and basic research, terms such as “endophenotype” and...
### TABLE 1: Animal Models of GEI in Schizophrenia

<table>
<thead>
<tr>
<th>Gene</th>
<th>Environmental Insult</th>
<th>Effects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INFECTION AND IMMUNITY MODELS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DISC1</td>
<td>Prenatal poly I:C</td>
<td>Synergistic increases in anxiety- and depressive-like behaviors</td>
<td>Abazyan et al. (2010)</td>
</tr>
<tr>
<td>DISC1</td>
<td>Early postnatal poly I:C</td>
<td>Synergistic impairment of short-term memory</td>
<td>Hikida et al. (2007) and Ibi et al. (2010)</td>
</tr>
<tr>
<td>DISC1</td>
<td>Prenatal poly I:C</td>
<td>Synergistic increase in IL-6, impaired novel object recognition and PPI</td>
<td>Smith et al. (2007) and Lipina et al. (2013)</td>
</tr>
<tr>
<td>Nurr1</td>
<td>Prenatal poly I:C</td>
<td>Synergistic impact on PPI, startle response, and latent inhibition</td>
<td>Vuillermot et al. (2011, 2012)</td>
</tr>
<tr>
<td>NRG1</td>
<td>Prenatal poly I:C</td>
<td>Several impacts: some additive, some with no combined effect</td>
<td>O’Leary et al. (2014)</td>
</tr>
<tr>
<td><strong>STRESS MODELS</strong></td>
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<tr>
<td>Reelin</td>
<td>Maternal separation</td>
<td>Protective effect of mutation on social motivation</td>
<td>Laviola et al. (2009), Ognibene et al. (2007), and Ognibene et al. (2008)</td>
</tr>
<tr>
<td>Nurr1</td>
<td>Social isolation, restraint stress</td>
<td>Synergistic impairment of PPI</td>
<td>Eells et al. (2006)</td>
</tr>
<tr>
<td>SEPT5</td>
<td>Social isolation</td>
<td>Protective effect of mutation on anxiety like behaviors</td>
<td>Harper et al. (2012)</td>
</tr>
<tr>
<td>PACAP</td>
<td>Social isolation vs environmental enrichment</td>
<td>Synergistic elevation of aggression and impact on PPI</td>
<td>Ishihama et al. (2010)</td>
</tr>
<tr>
<td>DISC1</td>
<td>Social isolation</td>
<td>Synergistic increases in locomotion, immobility in FST, and PPI deficiencies</td>
<td>Niwa et al. (2013)</td>
</tr>
<tr>
<td>DISC1</td>
<td>Chronic social defeat</td>
<td>Opposite effects of social defeat stress on mutant vs WT in tests of anxiety, synergistic effect on PPI and social interaction</td>
<td>Haque et al. (2012)</td>
</tr>
<tr>
<td>GAD</td>
<td>Maternal stress</td>
<td>Synergistic effects on fetal cortisol and birth weight</td>
<td>Uchida et al. (2014, 2011)</td>
</tr>
<tr>
<td>SNAP25 (bdr)</td>
<td>Maternal stress</td>
<td>Synergistic effects on sociability and PPI</td>
<td>Oliver and Davies (2009)</td>
</tr>
<tr>
<td>NRG1</td>
<td>Social stress</td>
<td>Additive effects on locomotion, memory, sociability, and synergistic effect on brain cytokine levels</td>
<td>Desbonnet et al. (2012)</td>
</tr>
<tr>
<td><strong>DRUG EXPOSURE MODELS</strong></td>
<td></td>
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<tr>
<td>COMT</td>
<td>Cannabis</td>
<td>Additive decreases in size and density of dopaminergic cells</td>
<td>Behan et al. (2012)</td>
</tr>
<tr>
<td>COMT</td>
<td>Cannabis</td>
<td>Additive increase in startle response, PPI deficit, and decreases in anxiety</td>
<td>O’Tuathaigh et al. (2010, 2012)</td>
</tr>
<tr>
<td>NRG1</td>
<td>Cannabis</td>
<td>Synergistic reduction of locomotor activity, increased anxiety, and impact on PPI</td>
<td>Boucher et al. (2007) and Long et al. (2013)</td>
</tr>
<tr>
<td>DISC1</td>
<td>Methamphetamine</td>
<td>Mutation blunted response to methamphetamine, synergistic attenuated response to conditioned place preference</td>
<td>Pogorelov et al. (2012)</td>
</tr>
<tr>
<td><strong>TOXIN EXPOSURE MODELS</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Reelin</td>
<td>Prenatal chlorpyrifos</td>
<td>Protective impact of toxic exposure on ultrasonic vocalization and on stimulant response</td>
<td>Scattoni et al. (2009), Laviola et al. (2006), and Mullen et al. (2013)</td>
</tr>
<tr>
<td>DISC1</td>
<td>Prenatal lead</td>
<td>Synergistic increases in anxiety like behaviors and in response to MK-801 administration</td>
<td>Abazyan et al. (2014) and Guilarte (2009)</td>
</tr>
</tbody>
</table>

GEI, gene–environment interaction; poly I:C, polyinosine-polycytidylic; IL, interleukin; PPI, prepulse inhibition; FST, forced swim test; WT, wild-type.
“intermediate phenotype” have been introduced (Donaldson & Hen, 2014). How the endophenotype concept has been shaping GEI animal models has been recently reviewed (Kannan et al., 2013). Briefly, the next generation of animal models should expand use of physiological and neural circuitries intermediate phenotypes, genome-wide gene expression, and epigenetic modification profiling in specific cell types (e.g., neurons vs astrocytes). We believe that utilization of standard endophenotypic measures may not only help minimize variability in effects of GEI but also bring in new model organisms to study the molecular mechanisms of GEI across species (e.g., worms, fruit flies, and zebrafish).

We need to take our animal models beyond studying a single pathophysiological process involved in GEI even if we model an interaction with a single adverse event. For example, in addition to the hypothalamus-pituitary-adrenal axis, studies of stress exposure should include the immune response to stressful stimuli (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 GEI models, including the immune responses taking place in the intestinal tract (Miller, Boulter, Ikin, & Smith, 2009).

Practically all basic (and human) GEI studies have been performed in candidate risk factors, the majority of which have not been confirmed by the recent GWAS (McCarroll, Feng, & Hyman, 2014; Nestler & Hyman, 2010). Although GEI studies based on rare highly penetrants mutations will likely remain the mainstream direction for years to come, there is an emergence of new models that incorporate polymorphisms identified by the Psychiatric Genomics Consortium (Quednow, Brzoza, & Rossner, 2014).

It is important to take developmental considerations into account when interpreting environmental effects that vary across different time points (Moffitt, Caspi, & Rutter, 2005; Rutter, 2008). In the past, addressing time-dependent interaction in GEI 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 MIA (Abazyan et al., 2011).

Combining an environmental challenge with a genetic mutation can produce diverse effects. Appearance of new brain and behavioral phenotypes, 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 a most prominent example of such a possibility (Blackwood et al., 2001).

The focus of most published GEI research has been on risk factors. However, the contribution of protective factors is also important and has so far been relatively neglected, although there are some exceptions. Identification of genes conferring resilience to schizophrenia-related abnormalities is a new emerging research to uncover unrecognized molecular targets (Mihali, Subramani, Kaunitz, Rayport, & Gaisler-Salomon, 2012). In this context, the role for environmental enrichment in ameliorating/rescuing genetically produced abnormalities has been recently reviewed (Pratt et al., 2012; Takuma et al., 2011).

New models with mutations in regulatory elements in candidate genes with more subtle regional, cell type- and time-specific manipulations, or human genetic variants knock-in models will better reflect the complex genetic and molecular mechanisms of schizophrenia (Papaleo, Lipska, & Weinberger, 2012). Therefore, time-dependent or circuitry- or cell-specific manipulations to target mRNA and/or proteins should be used.

Most studies have focused on neuronal functions of susceptibility genes. However, these genes are also expressed by glial cells (Iijima et al., 2009; Prevot et al., 2003). Given growing interest in the role for glia cells in mediating the effects of stress and microbial pathogens, GEI 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).

In conclusion, GEI animal models have already begun to provide new insights into the etiological complexity and heterogeneity of schizophrenia. We believe GEI animal models will continue to be a crucial tool to advance our knowledge about this debilitating disease and help searching for new treatment options.

Acknowledgments
We thank the following funding agencies for the support: MH-083728, MH-094268 Silvo O. Conte center and the Brain and Behavior Research Foundation, and Tabakman Trust Gift Grant (MVP).

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