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REVIEW

Neurodevelopment, GABA System Dysfunction, and Schizophrenia

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The origins of schizophrenia have eluded clinicians and researchers since Kraepelin and Bleuler began documenting their findings. However, large clinical research efforts in recent decades have identified numerous genetic and environmental risk factors for schizophrenia. The combined data strongly support the neurodevelopmental hypothesis of schizophrenia and underscore the importance of the common converging effects of diverse insults. In this review, we discuss the evidence that genetic and environmental risk factors that predispose to schizophrenia disrupt the development and normal functioning of the GABAergic system.

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INTRODUCTION

Schizophrenia is a devastating neuropsychiatric disorder that affects approximately 1% of the population. Its core symptoms fall into three domains: positive symptoms such as psychosis, negative symptoms such as poor social function, and cognitive symptoms such as deficient working memory and attention. Onset is typically in late adolescence or early adulthood, but signs of dysfunction can be seen in an earlier prodromal phase (Lewis and Levitt, 2002). Based on the clinical progression and the 64–81% heritability of the disorder (Giusti-Rodriguez and Sullivan, 2013), a hypothesis emerged that schizophrenia's origins could be found early in development, long before the onset of symptoms (Weinberger, 1987). For more than 35 years, clinicians and scientists have searched for the biological foundations of an altered developmental trajectory that leads to the specific disease symptoms, but our understanding of this process is far from complete.

Accumulating evidence from clinical, genetic, and epidemiologic studies over the past several decades supports the neurodevelopmental origin of schizophrenia and has begun to identify specific disturbances of brain development that might be pivotal for the emergence of the disease (Lewis and Levitt, 2002; Marenco and Weinberger, 2000; Rapoport *et al*, 2012). The data have identified numerous factors that increase risk of diagnosis (to be discussed), yet it is clear that none of these pathological processes alone can be identified as a singular cause of the disorder.

The genetics of schizophrenia are extremely complex. Over the past two decades, genetic studies of candidate genes implicated multiple disease-predisposing DNA sequence variants in disrupted-in-schizophrenia 1 (*DISC1*), neuregulin 1 (*NRG1*), catechol-*O*-methyl transferase (*COMT*), regulator of G-protein signaling 4 (*RGS4*), metabotropic glutamate receptor 3 (*GRM3*), dysbindin (*DTNBP1*), *G72*, and other sequences (Harrison and Weinberger, 2005), yet replications of these findings were quite inconsistent from cohort to cohort. More recently, genome-wide association studies (GWAS) analyzing DNA from tens of thousands of patients with schizophrenia have been identified between one and 'several thousands of common alleles of very small effect' associated with diagnosis (Aberg *et al*, 2013; Cross-Disorder Group of the Psychiatric Genomics C, Genetic Risk Outcome of Psychosis C, 2013; McAllister, 2014; Purcell *et al*, 2009; Ripke *et al*, 2013; Shi *et al*, 2009; Stefansson *et al*, 2009), yet these findings showed only a modest overlap with the outcomes of the candidate gene studies. With the expansion of the patient cohorts and development of more sophisticated analytical approaches, the newest GWAS data argue that diverse common alleles accumulate within a pathway and reach a threshold for susceptibility that leads to disease (Horvath and Mirnics, 2014b). Furthermore, it also appears that rare copy number variants with potentially large effect sizes might have an important role in predisposing to schizophrenia. These deletions or duplications of chromosomal regions often span multiple genes and can either

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increase risk or protect from diagnosis, presumably by altering the 'dosing' of the genes contained within the variant region (Grozeva *et al*, 2010; International Schizophrenia C, 2008; Stefansson *et al*, 2008). For example, 22q11 hemideletion is associated with high rates of schizophrenia (Gothelf *et al*, 1997; Karayiorgou *et al*, 2010; Murphy *et al*, 1999), whereas 22q11 duplication may protect against schizophrenia diagnosis (Rees *et al*, 2014), suggesting that expression levels of specific genes are critical to normal and pathological brain development.

Epidemiologic studies similarly identified various environmental disturbances that confer increased brain disease risk, but do not singularly cause the disorder (Sullivan *et al*, 2003; Tsuang, 2000; van Os *et al*, 2010). There is evidence that prenatal maternal immune activation (MIA) (Brown and Derkits, 2010), perinatal hypoxia (Cannon *et al*, 2002; Schmidt-Kastner *et al*, 2012), adolescent cannabis use (Arseneault *et al*, 2004; Henquet *et al*, 2008), stress (Norman and Malla, 1993), obstetric complications (Dalman *et al*, 1999), urbanicity (Vassos *et al*, 2012), migrant status (Cantor-Graae and Selten, 2005), advanced paternal age (Malaspina, 2001), and others (Brown, 2011; Tandon *et al*, 2008) interact with predisposing genetics to increase risk for illness.

Therefore, genetic and environmental influences alone may confer risk for schizophrenia, but it appears that a combination of multiple factors is necessary for disease manifestation in most cases (Giusti-Rodriguez and Sullivan, 2013; Lewis and Levitt, 2002; Mowry and Gratten, 2013; Sullivan *et al*, 2003; Tsuang, 2000). Supported by expanded basic science efforts and increasingly sophisticated animal models, a unifying concept has emerged stating that many of these disparate risk factors converge onto common dysfunctional pathways and lead to illness (Chen *et al*, 2013; de Jong *et al*, 2012; Horvath and Mirnics, 2009, 2014b; Mirnics *et al*, 2006). In this review, we discuss the concept that GABA system development is a major convergence point for genetic and environmental susceptibility factors for schizophrenia.

CORTICAL DEVELOPMENT

Early in mammalian development, the telencephalon emerges from the anterior portion of the neural tube and develops into the cortex and hippocampus. The plethora of cell types in the adult brain arise from progenitor pools in distinct subregions of the developing brain that are established as early as the morphogenic patterning of the neural tube (Bystron *et al*, 2008; Marin and Rubenstein, 2003). Progenitors in the subventricular zone that produce projection neurons express diverse combinations of transcription factors that guide them from proliferation through differentiation into unique types of cells (Greig *et al*, 2013; Molyneaux *et al*, 2007). Similarly, GABAergic interneuron types are predetermined based on unique transcription factor combinations in different progenitor types in the subpallial ganglionic eminences (Flames *et al*, 2007; Wonders and Anderson, 2006). However, migration patterns of glutamatergic projection neurons and GABAergic interneurons are quite different: while projection neurons migrate radially and remain in the general area where they were born, interneurons have a predominantly tangential migration, and integrate into regions far away from their origins (Bystron *et al*, 2008; Guo and Anton, 2014; Marin and Rubenstein, 2003; Nadarajah and Parnavelas, 2002).

Cajal–Retzius cells are interneurons that are among the first-born cells in the developing cortex and hippocampus. At the beginning of cortical expansion, they migrate into the cortical preplate (Bielle *et al*, 2005) and coordinate the organization of radial glia and migrating projection neurons by secreting reelin (RELN) (Tissir and Goffinet, 2003). RELN signals new projection neurons migrating along radial glia to bypass earlier-born neurons and layer in an 'inside-out' manner (Hashimoto-Torii *et al*, 2008; Tissir and Goffinet, 2003). The radial glia, meanwhile, are maintained by NRG1/ErbB signaling and even transient disruptions of NRG1 signaling cause these cells to differentiate prematurely, which could have a profound impact on radial migration (Schmid *et al*, 2003). GABAergic interneurons destined for the cortex, however, migrate tangentially over much longer distances from the subpallium, avoid the striatum via semaphorin 3A- and 3F-mediated chemorepulsion (Marin *et al*, 2001b), and settle into final positions after the migration of projection cells is compete (Bartolini *et al*, 2013; Pla *et al*, 2006). NRG1/ErbB interactions are necessary for GABAergic cell migration as neuregulin acts as both a local and long-range attractant cue for migrating interneurons and dysfunction of either ligand or receptor leads to deficits in cell migration and cortical patterning (Flames *et al*, 2004). Once they reach the cortex, interneuron populations tend to cluster together in specific layers (Ciceri *et al*, 2013), likely via cell type-specific expression of cell adhesion molecules including ErbB4 (Fazzari *et al*, 2010). Thus, interneuron integration into cortical lamina appears to be a tightly regulated spatial–temporal process.

Neuronal differentiation, migration, and integration are managed by a number of well-studied molecular processes. Brain-derived neurotrophic factor (BDNF) and other neurotrophins promote cellular migration, synaptogenesis, dendritic extension, and synaptic maintenance throughout life (Behar *et al*, 1997; Huang and Reichardt, 2001; Marin and Rubenstein, 2001a; Park and Poo, 2013). Altering levels of BDNF in the developing brain can disrupt the migration of both projection neurons and interneurons (Knusel *et al*, 1994; Polleux *et al*, 2002; Woo and Lu, 2006) and their coordinated extension and retraction of dendrites (McAllister *et al*, 1997). In addition to establishing cortical circuits, these functions of BDNF continue to be critical when synapses are strengthened or pruned later in development (Gorski *et al*, 2003; Vicario-Abejon *et al*, 2002) at a critical time for susceptibility for psychiatric disease (Paus *et al*, 2008). Therefore, maintaining appropriate local levels

of BDNF and other neurotrophins is critical at multiple points in development from neural progenitor stages to adolescent brain maturation.

RELN, NRG1/ErbB4, and BDNF are critical for the establishment of GABAergic circuitry. Defects in these pathways early in development could have cascading consequences due to GABA's own role as a trophic factor during cortical development (Owens and Kriegstein, 2002).

DEVELOPMENT OF THE GABAergic SYSTEM

GABA is the major inhibitory neurotransmitter in the brain; however, $GABA_A$ receptor activation is excitatory before birth (Ben-Ari, 2002). Tonic GABA release early in development (Cellot and Cherubini, 2013; Manent *et al*, 2005) stimulates and guides the migration of new projection neurons in a receptor type-dependent manner (Owens and Kriegstein, 2002). $GABA_A$ receptors are expressed on neural progenitors in the proliferative zone where GABA signaling promotes cell cycle exit and migration (LoTurco *et al*, 1995). $GABA_B$ and $GABA_C$ stimulation maintains migration through the cortical plate (Behar *et al*, 2001), whereas additional $GABA_A$ activation provides a stop signal (Behar *et al*, 2000). This entire process is highly orchestrated by dynamic expression of receptors during migration (Maric *et al*, 2001). Once in place, continued $GABA_A$ stimulation signals new projection neurons to extend processes (Barbin *et al*, 1993; Marty *et al*, 1996) and integrate into developing circuitry through new synaptic contacts (Wang and Kriegstein, 2008) while also regulating the maturation of inhibitory contacts (Wu *et al*, 2012). Increasing potassium chloride cotransporter 2 (KCC2) expression around the time of birth switches the chloride gradient from depolarizing to hyperpolarizing; however, there is evidence that local chloride gradients may be different at certain interneuron synapses and in disease states (Arion and Lewis, 2011; Hyde *et al*, 2011). These processes continue to guide migration and integration in the dentate gyrus of the hippocampus where neurogenesis continues into adulthood (Ge *et al*, 2006).

The final product of development is a diverse population of interneurons, each serving a different function. Mature interneurons can be distinguished by their molecular content, electrical properties, synaptic targets and laminar distributions (Ascoli *et al*, 2008; DeFelipe *et al*, 2013; Markram *et al*, 2004). Interneuron cell types typically contain either the calcium binding proteins, such as parvalbumin (PV), calretinin (CR), or calbindin (CB), or the neuropeptides, such as cholecystokinin (CCK), neuropeptide Y (NPY), somatostatin (SST), or vasointestinal peptide (VIP), but occasionally contain more than one of these markers (Ascoli *et al*, 2008; Markram *et al*, 2004). PV+ cells are fast-spiking basket and chandelier cells that innervate pyramidal cell soma and axon initial segments, respectively (Markram *et al*, 2004), as well as other interneuron populations (Lovett-Barron *et al*, 2012). Another type of basket cells, containing CCK, also form perisomatic contacts onto pyramidal cells; however, they are distinguished from the PV+ variety by their slower, accommodating firing patterns (Hefft and Jonas, 2005) that integrate neuromodulatory information with faster network activity (Freund, 2003; Varga *et al*, 2009). Interconnected networks of NPY+ neurogliaform cells mediate regional tonic inhibition through extrasynaptic volume transmission in multiple cortical and subcortical regions (Manko *et al*, 2012; Olah *et al*, 2009; Price *et al*, 2005). Martinotti cells, containing CR, CB, SST, NPY, and/or CCK, span both cortical lamina and cortical columns and synapse onto pyramidal cell tuft dendrites in layer I (Markram *et al*, 2004). Bipolar and double bouquet cells are found in multiple cortical lamina and primarily synapse onto pyramidal cell dendrites and other interneurons and express some combination of CCK, CR, CB, or VIP, whereas bitufted cells are similar in their synaptic contacts and function, but can also express NPY or SST (Markram *et al*, 2004). A subset of these cells expressing VIP are particularly interesting because they regulate PV+ and SST+ interneurons to disinhibit cortical circuits (Pi *et al*, 2013). While these are common generalized examples, interneuron cell types are, in fact, so diverse that they can be further subdivided using numerous features (Ascoli *et al*, 2008). For example, 21 types of interneurons regulate the function of only three types of glutamatergic cells in the hippocampus (Klausberger and Somogyi, 2008). This diversity and integration within networks highlights the importance of coordinated interneuron development and function in multiple brain regions.

Brain development requires precise coordination and timing of many contributing molecular systems. Any disruption could offset, alter, or cease these coordinated processes with immediate, delayed, or cascading consequences on brain function and alter the trajectory of development (Lewis and Levitt, 2002). Depending on the timing of the insult, common disruptions could have transient effects or marked and compounding consequences that lead to chronic disability (Horvath and Mirnics, 2014a; Insel, 2010; Lewis and Levitt, 2002). Furthermore, the individual genetic makeup appears to be critical: the same insult can have minimal effect or a large effect in two different individuals, and this will largely depend on the disease-predisposing sequence variants in their genome (Horvath and Mirnics, 2014b).

ANATOMICAL AND HISTOLOGICAL FINDINGS SUGGEST NEURODEVELOPMENTAL DYSFUNCTION OF CELL MIGRATION AND SYNAPTIC INTEGRATION IN SCHIZOPHRENIA

In addition to the clinical progression of symptoms across adolescent and adult development (Insel, 2010; Lewis and Lieberman, 2000), clues connecting neurodevelopmental

dysfunction with schizophrenia can be found in post-mortem brain tissue from patients with the disorder. Perhaps, the best documented anatomical findings are reduced cortical thickness and enlarged ventricles (Harrison, 1999). However, the lack of degenerative pathology suggests that these findings are due to abnormalities in cellular migration and/or neuronal arborization and synaptic function (Folsom and Fatemi, 2013; Harrison, 1999; Marenco *et al*, 2000; Selemon and Goldman-Rakic, 1999). Several cellular and molecular findings support this view and provide evidence for neurodevelopmental abnormalities long before the onset of illness.

Differences in cellular distribution are often attributed to altered neuronal migration early in brain development (Metin *et al*, 2008). Altered neuronal densities were reported in the prefrontal cortex (Akbarian *et al*, 1996; Anderson *et al*, 1996; Connor *et al*, 2009; Daviss and Lewis, 1995; Ikeda *et al*, 2004; Joshi *et al*, 2012; Morris *et al*, 2008; Rajkowska *et al*, 1998; Selemon *et al*, 1995, 1998, 2003; Yang *et al*, 2011), auditory cortex (Dorph-Petersen *et al*, 2009), cingulate cortex (Benes, 1991, 1993; Brune *et al*, 2010; Connor *et al*, 2009), entorhinal cortex (Arnold *et al*, 1991; Falkai *et al*, 2000; Jakob and Beckmann, 1986; Kovalenko *et al*, 2003; Wang *et al*, 2011), fusiform cortex (Di Rosa *et al*, 2009), occipital cortex (Selemon *et al*, 1995), parietal cortex (Chance *et al*, 2005), visual cortex (Dorph-Petersen *et al*, 2007), thalamus (Young *et al*, 2000), hypothalamus (Bernstein *et al*, 1998), striatum (Kreczmanski *et al*, 2007), amygdala (Kreczmanski *et al*, 2007), and hippocampus (Konradi *et al*, 2011) in post-mortem brain tissue from schizophrenic patients. Interestingly, many of these reports show specific defects in GABAergic interneuron density or distribution (Benes *et al*, 1991; Chance *et al*, 2005; Daviss and Lewis, 1995; Di Rosa *et al*, 2009; Ikeda *et al*, 2004; Joshi *et al*, 2012; Konradi *et al*, 2011; Morris *et al*, 2008; Wang *et al*, 2011; Yang *et al*, 2011). While the majority of studies report decreased cell densities, others argue the opposite or find no change (Beasley *et al*, 2009; Cullen *et al*, 2006; Heckers *et al*, 1991; Pennington *et al*, 2008; Smiley *et al*, 2012).

Interstitial white matter neurons (IWMNs) have also been particularly well studied. IWMNs are neurons in white matter tracts that remain from the early cortical subplate zone (Chun and Shatz, 1989) or GABAergic interneurons from the ganglionic eminences (Anderson *et al*, 2001). The density of these cells typically declines during development as migration is completed and the subplate disappears (Connor *et al*, 2009; Kostovic and Rakic, 1990; Meyer *et al*, 1992). Several studies have reported changes in the distribution of superficial and/or deep IWMNs in the cortices of subjects with schizophrenia. However, like the cell density studies, these data do not form a consensus. Some studies report increased density in the superficial white matter (Anderson *et al*, 1996; Connor *et al*, 2009; Eastwood and Harrison, 2005; Joshi *et al*, 2012; Kirkpatrick *et al*, 1999, 2003; Yang *et al*, 2011), whereas others report decreased density in superficial, but increased or variable density in deep white matter (Akbarian *et al*, 1993a, b, 1996). Variation in patient populations, brain regions, or methodologies (such as particular molecular markers used to identify cells) may account for these discrepancies (Connor *et al*, 2009; Eastwood and Harrison, 2005; Harrison, 1999; Heckers, 1997; Meyer *et al*, 1992). Regardless of the reported differences, the most likely explanation for the displacement of IWMNs is that cellular migration of GABAergic interneurons and/or their cell death are disrupted very early in development.

In summary, the anatomical and histological findings in schizophrenia suggest that altered cellular migration and synaptic formation are an important part of the disease process, and that GABA system-associated genes are particularly affected in this cascade of deleterious events. This view is also supported by molecular studies in post-mortem tissue from patients with schizophrenia and mechanistic studies in animal models (to be discussed).

GENE EFFECTS CONVERGE ONTO GABA SYSTEM DEVELOPMENT

In addition to cellular evidence, changes in the expression of genes with known importance for developmental processes—including cellular migration, synaptogenesis, synaptic maintenance, cell signaling, glia, immune regulation, and mitochondrial function—have been found in post-mortem tissue from patients with schizophrenia (Arion *et al*, 2007, 2010; Clay *et al*, 2010; Hakak *et al*, 2001; Harrison and Weinberger, 2005; Horvath and Mirnics, 2014a, b; Jaaro-Peled *et al*, 2009; Lewis *et al*, 2005; McGlashan and Hoffman, 2000; Middleton *et al*, 2002; Mirnics *et al*, 2000, 2001b; Mirnics and Pevsner, 2004; Roussos *et al*, 2012). Importantly, multiple studies report expression changes in GABA system-related transcripts, including altered expression of GABA-synthesizing enzymes, glutamic acid decarboxylase 1 and 2 (*GAD1* and *GAD2*, discussed in the next section), interneuron-expressed proteins and neuropeptide genes (*PV*, *CCK*, *NPY*, *SST*, and *CB*) (Hashimoto *et al*, 2003, 2008a; Hoftman *et al*, 2013; Iritani *et al*, 2000; Kuromitsu *et al*, 2001; Maldonado-Aviles *et al*, 2009; Mellios *et al*, 2009; Volk *et al*, 2012), GABA receptor subunits (*GABRA1–2*, *GABRA4–6*, and *GABRD*) (Benes *et al*, 1992; Hashimoto *et al*, 2008a, b; Hoftman *et al*, 2013; Maldonado-Aviles *et al*, 2009; Volk *et al*, 2002b), and interneuron development- and maintenance-related mRNAs (GABA transporter 1, sodium potassium chloride cotransporter 1 (*NKCC1*), and *KCC2*) (Arion *et al*, 2011; Fish *et al*, 2011; Hashimoto *et al*, 2008a, b; Hoftman *et al*, 2013; Hyde *et al*, 2011; Volk *et al*, 2002b). Of these, the current review will focus primarily on the *GAD1* deficit and its relationships with *RELN*, *BDNF*, *NRG1*, and *DISC1*.

Deficiencies in *GAD1* expression, the enzyme responsible for producing the majority of the GABA in the brain, are commonly found in many brain regions in post-mortem

tissue from patients with schizophrenia (Akbarian and Huang, 2006; Akbarian *et al*, 1995; Costa *et al*, 2004; Curley *et al*, 2011; Fatemi *et al*, 2005; Guidotti *et al*, 2000a; Hashimoto *et al*, 2003, 2008a, b; Huang and Akbarian, 2007; Impagnatiello *et al*, 1998; Kalkman and Loetscher, 2003; Knable *et al*, 2002; Lewis *et al*, 2005; Mirnics *et al*, 2000; Thompson Ray *et al*, 2011; Volk *et al*, 2000; Volk and Lewis, 2002a). Interestingly, *GAD1* mRNA was not detectable in approximately 30% of GABAergic interneurons in the cortex of post-mortem brains from individuals with schizophrenia (Akbarian *et al*, 1995; Volk *et al*, 2000), whereas cells with detectable GAD1 appeared to have normal levels (Volk *et al*, 2000), suggesting dysregulation of GABAergic gene expression is cell type-specific. However, this does not mean that the majority of interneurons are unaffected by the disease process. Reductions of interneuronal-expressed genes *NPY*, *SST*, *CCK*, and *PV* have been found repeatedly in the cortex of subjects with schizophrenia in post-mortem studies (Hashimoto *et al*, 2003, 2008a; Hoftman *et al*, 2013; Ikeda *et al*, 2004; Iritani *et al*, 2000; Kuromitsu *et al*, 2001; Maldonado-Aviles *et al*, 2009; Mellios *et al*, 2009; Volk *et al*, 2012). Deleting *GAD1* in animal models causes catastrophic effects on development by almost completely reducing brain GABA content and is not compatible with life (Asada *et al*, 1997). However, *GAD1* suppression in limited periods of development or in restricted cell types has multiple consequences. Disrupting GABA signaling during early development alters cellular migration and cortical architecture in cell type-dependent ways (Aronne *et al*, 2011; Cuzon *et al*, 2008; Haas *et al*, 2013; Manent *et al*, 2007; Thompson *et al*, 2009; Wu *et al*, 2012). PV+ interneurons are selectively disrupted by exogenous GABA potentiation (Haas *et al*, 2013; Levav-Rabkin *et al*, 2010). During adolescence, when cells have finished migrating and cortical circuits are maturing, *GAD1* suppression decreases axonal branching in PV+ cells in a cell autonomous manner (Chattopadhyaya *et al*, 2007) and increases pyramidal cell activity (Lazarus *et al*, 2013). Adult mice with *GAD1* gene expression deficits in restricted interneuron populations have distinct molecular and behavioral dysfunction depending on the affected cell type (Brown *et al*, 2013; Kvitsiani *et al*, 2013; Schmidt *et al*, 2013). These data provide functional context to post-mortem studies that consistently implicate diverse interneuron cell types in schizophrenia (Hashimoto *et al*, 2003, 2008a; Hoftman *et al*, 2013; Iritani *et al*, 2000; Kuromitsu *et al*, 2001; Maldonado-Aviles *et al*, 2009; Mellios *et al*, 2009; Morris *et al*, 2008; Volk *et al*, 2012) and suggest that GABAergic gene expression deficits seen in post-mortem studies of patients with schizophrenia actively contribute to important aspects of brain development and behavior (Lewis *et al*, 2005; Marin, 2012; Schmidt and Mirnics, 2012).

As mentioned previously, RELN is critical for the migration and laminar organization of the cortex and hippocampus. *RELN* is expressed in Cajal–Retzius cells during early development and from many GABAergic cells in multiple cortical layers shortly after birth (Alcantara *et al*, 2006). Brain tissue from schizophrenic patients also consistently report decreased expression of the *RELN* gene (Eastwood and Harrison, 2006; Fatemi *et al*, 2000, 2001; Folsom and Fatemi, 2013; Guidotti *et al*, 2000a; Habl *et al*, 2012; Impagnatiello *et al*, 1998; Maloku *et al*, 2010; Ruzicka *et al*, 2007), which is likely the result of altered genetic and/or epigenetic regulation (Costa *et al*, 2003; Grayson *et al*, 2005, 2006; Tochigi *et al*, 2008; Veldic *et al*, 2004, 2007). While the *RELN* deficiency observed in post-mortem tissue clearly does not impact cortical architecture to the same degree as total *RELN* loss during cortical development, it is likely that even a small reduction of RELN would affect synaptic integration during development and/or synaptic stability and plasticity in adulthood (Frotscher, 2010). It is also likely that the ontogeny of this deficit varies from patient-to-patient. RELN was initially discovered as a mutation affecting cortical development and behavior in reeler mice (reviewed by (Folsom and Fatemi, 2013; Lambert de Rouvroit and Goffinet, 1998; Tissir and Goffinet, 2003) and has been studied extensively in other systems and clinical populations. In addition to being a necessary component of cortical development, RELN also has a role in stabilizing neurons and synapses throughout life (Abraham and Meyer, 2003; Frotscher, 2010; Guidotti *et al*, 2000b). It is expressed by GABAergic interneurons and the expression of the *GAD1* and *RELN* genes is tightly coordinated by a common epigenetic mechanism (Costa *et al*, 2004; Grayson *et al*, 2005, 2006; Guidotti *et al*, 2000a; Impagnatiello *et al*, 1998; Kundakovic *et al*, 2009; Maloku *et al*, 2010; Noh *et al*, 2005; Pesold *et al*, 1999; Rodriguez *et al*, 2002; Ruzicka *et al*, 2007; Tochigi *et al*, 2008; Veldic *et al*, 2004, 2007). In addition, rodent models show that *RELN* deficiency alone can result in downstream reductions of both *GAD1* (Kutiyanawalla *et al*, 2012; Nullmeier *et al*, 2011; Pascual *et al*, 2004; Takayama, 1994) and *BDNF* (Pillai and Mahadik, 2008). Thus, it appears that RELN and GABAergic deficits in schizophrenia are tightly linked.

A similar decrease in BDNF has been observed consistently in several studies (Hashimoto *et al*, 2005; Mellios *et al*, 2009; Thompson Ray *et al*, 2011; Toyooka *et al*, 2002; Weickert *et al*, 2003). Genetic variants of the *BDNF* gene associated with schizophrenia (Neves-Pereira *et al*, 2005) produce progressive cortical and hippocampal structural changes, as well as behavioral impairment (Egan *et al*, 2003a; Pezawas *et al*, 2004). A genetic variant of *BDNF* associated with increased risk for psychiatric disorders including schizophrenia (Egan *et al*, 2003b; Gratacos *et al*, 2007) is linked to reduced cortical and hippocampal volumes and impaired learning and memory, presumably by interfering with the development and maintenance of neurons and synapses (Egan *et al*, 2003b; Eisenberg *et al*, 2013; Hariri *et al*, 2003; Pezawas *et al*, 2004; Szeszko *et al*, 2005; Tost *et al*, 2013). However, these findings are not always replicated and more studies are needed to clarify the mechanisms of the Val66Met allele and psychiatric illness (Kanazawa *et al*, 2007). Animal studies show that BDNF is also vital for developing GABAergic circuitry, controlling

everything from interneuron migration to establishing synaptic contacts (Danglot *et al*, 2006; Ikeda *et al*, 2006; Ohba *et al*, 2005; Yamada *et al*, 2002), positioning and activating RELN-secreting Cajal–Retzius cells (Alcantara *et al*, 2006; Ringstedt *et al*, 1998), regulating GABA release probability (Ohba *et al*, 2005), and expressing GAD1 (Huang *et al*, 1999; Ohba *et al*, 2005; Yamada *et al*, 2002). Conversely, GABA regulates BDNF through activity-dependent processes that switch from inducing to inhibiting *BDNF* gene expression around the same time GABA signaling switches from excitatory to inhibitory (Berninger *et al*, 1995). PV-expressing (PV+) interneurons were hypothesized to be the main target of BDNF-dependent processes (Hashimoto *et al*, 2005; Lewis *et al*, 2005) because PV+ interneurons express the BDNF receptor TrkB (Cellerino *et al*, 1996); however, the differentiation of NPY+ interneurons *in vitro* is also BDNF-dependent (Marty *et al*, 1996) and *in vivo* rodent studies demonstrate that BDNF is necessary for the expression of *NPY* and *SST* in the absence of any changes in *PV*, *GAD1*, or *GAD2* (Glorioso *et al*, 2006). These results closely mirror postmortem studies of schizophrenia that show tight correlations between *NPY*, *SST*, and *BDNF* gene expression (Hashimoto *et al*, 2008b; Mellios *et al*, 2009). It is possible, based on the GABAergic regulation of BDNF, that the developmental time points of *in vitro* and *in vivo* measurements in model systems could affect the interpretation of these and other results due to the changing influence of GABA signaling on activity-dependent processes across development. However, this prospect also highlights the very interesting possibility that risk factors for schizophrenia have different and even opposing consequences depending on the specific timing of the insult. Regardless, it is clear that BDNF and GABA systems interact extensively and deficits in either system may affect the other to a large degree, particularly during development.

NRG1 and its receptor ErbB4 have both been implicated in genetic susceptibility for schizophrenia in candidate gene studies (Harrison and Law, 2006; Mei and Xiong, 2008; Rico and Marin, 2011; Stefansson *et al*, 2004). *NRG1* mRNA is increased in the brains of schizophrenic patients along with its receptor ErbB4 (Chong *et al*, 2008; Harrison and Law, 2006; Hashimoto *et al*, 2004; Law *et al*, 2006, 2007) along with increased NRG1 protein intracellular domain (Chong *et al*, 2008) but decreased C-terminal fragment (Barakat *et al*, 2010), indicating abnormal proteolytic cleavage and dysfunctional NRG1 signaling. Animal studies have elaborated the importance of NRG1/ErbB in GABAergic interneuron migration and provided support for translatability of the findings. ErbB4 shows conserved interneuron-specific expression in mice, rats, monkeys, and humans (Neddens *et al*, 2011) and NRG1/ErbB4 signaling is necessary for the development of inhibitory circuits (Del Pino *et al*, 2013; Fazzari *et al*, 2010). Neddens *et al* (2011) also showed that ErbB4 expression was restricted to cells that express interneuron subclass markers PV, CCK, or CR, but not those that express CB, which is particularly interesting since CB interneurons are also those that appear to be unaffected in schizophrenia (Lewis *et al*, 2005). NRG1/ErbB4 signaling also appears to have distinct functions in development and maintenance of cortical circuitry. ErbB4 associates with $GABA_A\alpha1$ subunit-containing GABA receptors expressed on interneurons and NRG1/ErbB4 signaling reduces their surface expression (Mitchell *et al*, 2013), which likely contributes to increased excitability of interneurons by NRG1 (Li *et al*, 2012) and partially explains the mechanism behind increased GABA release and decreased pyramidal cell activity after NRG1 application (Wen *et al*, 2010). Fast-spiking PV+ interneurons are necessary for the generation of gamma oscillations and it is possible that these pathways underlie deficient oscillatory activity in schizophrenia (Hou *et al*, 2013; Lewis *et al*, 2012; Uhlhaas and Singer, 2010). However, *ERBB4* deletion in mice can lead to either impaired or increased gamma oscillations depending on the timing of the deletion. Genomic *ERBB4* deletion was accompanied by a ~30% reduction in the number of PV+ interneurons and lead to decreased oscillatory activity (Fisahn *et al*, 2009), whereas conditional deletion in postmitotic interneurons, albeit with residual expression due to low receptor turnover, displayed normal PV+ cell numbers and lead to increased oscillatory power (Del Pino *et al*, 2013), suggesting that reduced gamma oscillations in schizophrenia might arise from insults very early in development. Despite the evidence in favor of a common NRG1/ErbB4 signaling/PV+ interneuron dysfunction phenotype, restricting *ERBB4* deletion to PV+ interneurons did not account for all of the NRG1/ErbB4-associated behavioral abnormalities due to the presence of a large number of NRG1+/PV− cells in the amygdala (Shamir *et al*, 2012). This contrast is a quintessential example of how similar genetic insults lead to divergent phenotypes depending on their developmental timing and cell type-specific expression, as well as brain region-specific differences, and highlights the importance of GABAergic cell type-specific effects of genetic manipulations.

DISC1 was identified as a schizophrenia susceptibility gene in a pedigree of a Scottish family carrying a translocation that was associated with major mental illness (Muir *et al*, 2008; St Clair *et al*, 1990). Subsequent genetic and biological research has clarified the function of *DISC1* and its importance in development. *DISC1* associates with proteins that regulate microtubules and is necessary for normal cell migration and neurite outgrowth (Brandon and Sawa, 2011; Kamiya *et al*, 2005). It is also important for synaptic integration in the dentate gyrus in adulthood as *DISC1* knockdown produces abnormalities in neuronal positioning and synaptic contacts (Duan *et al*, 2007). These findings support the role of *DISC1* in developing synaptic connections in the cortex and hippocampus in schizophrenia, which have been elaborated in mice (Jaaro-Peled, 2009). Of particular interest for this review, activity-dependent GABAergic stimulation during early cortical development and during adult neurogenesis in the

hippocampus is critical for the *DISC1*-dependent regulation of neurite outgrowth and synaptic integration (Duan *et al*, 2007; Kim *et al*, 2012). This interaction between DISC1 and GABAergic systems is thought to underlie alterations in cortical volumes (Brauns *et al*, 2011; Duff *et al*, 2013; Mata *et al*, 2010; Trost *et al*, 2013) and hippocampal function (Callicott *et al*, 2013) in patients with *DISC1* risk alleles. Furthermore, the codependence of DISC1 and GABA in this period of development represents a point of convergence with other risk factors including NRG1 (Mata *et al*, 2010; Wood *et al*, 2009) and environmental exposures. Importantly, a dominant-negative *DISC1* mutation had differential effects on the brain and behavior depending on the specific timing of its expression during development (Ayhan *et al*, 2011), which reinforces the importance of the timing of developmental insults.

While extremely informative and irreplaceable, post-mortem research cannot determine if, when, or how specific gene expression deficits, environmental insults, or gene × environment interactions (G × E) incite their principal and cascading effects. Yet, the question of the developmental pathophysiological cascade is critical for understanding the disease: diverse genetic predispositions and various environmental insults, when combined, give rise to a set of common phenotypic manifestations that we classify as schizophrenia. Thus, understanding the convergence process that leads from etiological diversity to phenotypic similarity must be pursued through various *in vitro* and *in vivo* animal models, which has a potential for direct furthering clinical research and drug discovery (Harrison and Weinberger, 2005; Horvath *et al*, 2011; Horvath and Mirnics, 2009, 2014a; Levitt *et al*, 2006; Lewis and Mirnics, 2006; Mirnics *et al*, 2001b, 2006).

ENVIRONMENTAL INSULTS DISRUPT GABAergic SYSTEM DEVELOPMENT

The combination of anatomical, histological, and molecular findings in post-mortem tissue of subjects with schizophrenia is consistent with early neurodevelopmental disturbances. Importantly, gene expression is one of the initial points of interaction between genes and environment: cell signaling pathways initiated by environmental events appear to converge on transcriptional regulators to induce or inhibit the expression of specific genes (Harrison and Weinberger, 2005; Horvath *et al*, 2011; Horvath and Mirnics, 2009, 2014a, b; Levitt *et al*, 2006; Lewis and Mirnics, 2006; Mirnics *et al*, 2001b, 2006). Therefore, while gene expression changes can indicate either genetic or environmental disruptions, in the context of schizophrenia they likely represent a sum of G × E interactions. As mentioned previously, genetic susceptibility alone cannot account for the risk of schizophrenia diagnosis. The cumulative and interactive effects of genetic and environmental factors represent the remainder of the risk. Environmental factors exert their influences directly by affecting specific cellular processes (eg, toxins, fast cell signaling events, etc) or indirectly by manipulating the expression of genes (eg, hormones, drugs, immune system activation, modulatory cell signaling events, etc). The interaction between genetics and environment, through which a genetic predisposition is revealed, can explain how individuals with identical genetic makeup (ie, monozygotic twins) differ in subtle aspects of their appearance or personality, and in some cases in drastic aspects of their physical and mental health. For example, concordance rate for schizophrenia diagnosis in monozygotic twins is only about 50% (Cardno and Gottesman, 2000), suggesting that the remainder of risk for psychosis is attributable to other factors including environmental exposures. Animal models have been used to determine the mechanisms behind these environmental insults, G × E interactions, and brain development.

As mentioned previously, prenatal MIA, stress, cannabis use, and others have been established as environmental risk factors for schizophrenia (van Os *et al*, 2010). However, determining causality can be difficult because of the protracted amount of time between insult and diagnosis (Lewis and Levitt, 2002). Immune system activation has been implicated as a risk factor for schizophrenia (Horvath and Mirnics, 2014a) and the major histocompatibility complex is the most prominent signal in GWAS studies (McAllister, 2014; Stefansson *et al*, 2009). MIA in rats and mice causes dysfunction of GABAergic circuitry in the hippocampus, amygdala, and cortex (Canetta and Brown, 2012; Meyer, 2014). GABA content decreases (Bitanihirwe *et al*, 2010), GAD1 gene expression decreases (Deslauriers *et al*, 2013; Richetto *et al*, 2013), and GABA receptor subunit expression increases (Nyffeler *et al*, 2006) following immune activation during prenatal development. These effects appear to affect specifically PV+ interneurons (Ducharme *et al*, 2012; Ibi *et al*, 2010; Piontkewitz *et al*, 2012), although effects on other interneuronal cell types cannot be excluded. Rodent models have pinpointed interleukin-6 (IL-6) as the critical factor leading to molecular and behavioral dysfunction (Garbett *et al*, 2012; Smith *et al*, 2007), suggesting that modulating the IL-6 pathway for therapeutic development may be beneficial. Interestingly, a schizophrenia-associated missense mutation in the *NRG1* gene leads to increased *IL-6* gene expression and protein secretion in humans (Marballi *et al*, 2010). Furthermore, interferon-induced transmembrane protein 3 (*IFITM3*) expression in astroglia appears to be involved in mediating this MIA-IL-6 response (Ibi *et al*, 2013), which is interesting considering *IFITM3* is increased in schizophrenia and negatively correlated with GABAergic gene expression (Horvath and Mirnics, 2014a; Siegel *et al*, 2013). Furthermore, the delayed molecular and behavioral effects of MIA in adulthood can be revealed in at-risk genotypes as mice with mutant forms of *DISC1* display additional phenotypes after *in utero* exposure to polyinosinic:polycytidylic acid (poly I:C), a double-stranded RNA viral mimetic and cytokine inducer (Abazyan *et al*, 2010; Ibi *et al*, 2010; Lipina *et al*, 2013). The immune system, GABAergic

systems, and schizophrenia risk genes may be an important point of G × E interaction in schizophrenia. This concept is further supported by the previously mentioned influences of NRG1/ErbB4 and immune activation on the migration/function of PV + interneurons and the interaction between DISC1 and GABA on neuronal migration and synaptic formation.

Stress is also an important risk factor for schizophrenia (Weinberger, 1987) and animal models provide evidence that it potentiates the effects of other disease-predisposing factors. Stress during adulthood compounds the effects of *in utero* MIA exposure on GABAergic gene expression, including decreased expression of *GAD1*, and leads to dysfunctional behavior (Deslauriers *et al*, 2013; Giovanoli *et al*, 2013). Chronic social stress interacts with NRG1 deficiency to change inflammatory cytokine and *BDNF* gene expression (Desbonnet *et al*, 2012). Early life stress (Roth *et al*, 2009) or chronic social defeat stress (Tsankova *et al*, 2006) increases persistent methylation and decreases *BDNF* gene expression in rodents. While this result mirrors the decreased *BDNF* expression seen in patients, the Val66Met variant associated with psychosis is accompanied by less *BDNF* methylation in the PFC (Mill *et al*, 2008). Owing to the brain region- and promoter-specific nature of these effects (Wong *et al*, 2010), and differences in rodent and human neuroanatomy, more evidence will be required to understand the interaction between Val66Met, *BDNF* epigenetics, stress, and psychosis (Boulle *et al*, 2011). Chronic stress also interacts with the cannabinoid system to sensitize the effects of cannabinoids and shift cannabinoid-mediated control of plasticity from projection neurons to GABAergic cells (Patel *et al*, 2009; Reich *et al*, 2013). CCK + interneurons are the only interneuron cell type that expresses the cannabinoid receptor CNR1 (Eggan *et al*, 2010), which silences CCK + interneurons (Losonczy *et al*, 2004) and disrupts the hippocampus (Hajos *et al*, 2000; Katona *et al*, 1999) and amygdala (Katona *et al*, 2001; Tan *et al*, 2010) function. Furthermore, *GAD1* suppression in CCK + /CNR1 + interneurons leads to dysfunctional amygdala-dependent behavior and aminergic signaling (Brown *et al*, 2013; Schmidt *et al*, 2013). Finally, mild stress during development results in epigenetic-mediated reduction of dopaminergic cell function in *DISC1* mutant mice (Niwa *et al*, 2013), whereas the loss of *DISC1* in the frontal cortex of adult rats increased stress sensitivity and resulted in cognitive impairments that were not observed in rats with normal *DISC1* expression (Gamo *et al*, 2013). These results establish an important G × E interaction between *DISC1* and stress and reinforce the importance of developmental timing of this interaction.

In this manner, animal models provide the opportunity for linking data and understanding dynamically and reciprocally regulated functional and molecular networks. It is likely that immune activation, stress, and/or repeated cannabis exposure interact with genetic and/or molecular dysfunction, including GABA system genes, *NRG1*, *DISC1*, and others, to impair GABAergic circuitry to a greater degree than any aspect alone and lead to behavioral abnormalities.

FUTURE RESEARCH DIRECTIONS

Since the initial description of the neurodevelopmental hypothesis of schizophrenia, data from epidemiological, clinical, post-mortem, and animal model studies continue to support and extend its premise (Brandon and Sawa, 2011; Brown, 2011; Horvath and Mirnics, 2014a, b; Lewis and Levitt, 2002; Lewis and Mirnics, 2006; Michel *et al*, 2012; Mirnics *et al*, 2000, 2001b, 2006; Mirnics and Lewis, 2001a; Rapoport *et al*, 2012; Schmidt and Mirnics, 2012). Concurrently, GABAergic dysfunction has become recognized as a hallmark feature of the disorder. The number of studies reporting GABAergic dysfunction in the post-mortem brain of subjects with schizophrenia and the percentage of patients with *GAD1* deficits in these studies far surpasses the accountability of *GAD1* genetic variation. Rather, human data and animal models strongly argue that environmental insults, especially through immune system changes, converge with genetic susceptibility to alter GABAergic development and function, and contribute to behavioral impairment. However several questions remain unanswered and warrant further study.

First, *GAD1*, *RELN*, *BDNF*, *NRG1*, *DISC1*, and other genes with important developmental functions are regulated by activity-dependent processes, and this makes the expression changes found in post-mortem tissue from patients challenging to interpret. These alterations are either caused by specific disruptions of signaling events and transcriptional processes specific for each gene (Horvath and Mirnics, 2014b; Mirnics *et al*, 2001b) or are possibly adaptations to generic decreases in synaptic activity. As GABA is excitatory early in development and inhibitory after birth, changes in GABA system function should have opposing consequences on activity-dependent gene expression depending on when they occur. Recent studies showing that *NKCC1* and *KCC2*, the ion transporters responsible for the excitatory/inhibitory switch, are dysregulated in schizophrenia, further complicating the possible interpretational framework (Arion *et al*, 2011; Hyde *et al*, 2011; Tao *et al*, 2012). More studies are needed to determine how the specific developmental timing of environmental insults interact with genetic susceptibility, and we need a better understanding how altered chloride transporter expression in the adult brain impacts schizophrenia-relevant behaviors.

Second, the GABA system is incredibly diverse, making it difficult to determine what are the effects of specific GABAergic system deficits at the level of synaptic circuitry (Ascoli *et al*, 2008; DeFelipe *et al*, 2013). It appears that schizophrenia is characterized by dysfunction of multiple interneuronal cell types (Lewis *et al*, 2005). These deficits presumably interact at a level of neuronal networks, giving rise to complex behavioral phenotypes, yet we study them in

isolation. For example, PV+ chandelier cells regulate the output of cortical pyramidal cells across multiple areas (Markram *et al*, 2004; Woodruff *et al*, 2010). Their 'fast-spiking' activity is determined by their glutamatergic innervation and by expression of P/Q-type voltage-gated calcium channels, which cluster at synaptic active zones and support rapid vesicular release (Hefft and Jonas, 2005). However, this makes it difficult to determine whether PV+ interneurons are inherently dysfunctional in the pathophysiology of schizophrenia or whether activity-dependent deficits driven by the glutamatergic system are a more proximal disturbance. Since PV+ interneurons receive dense glutamatergic projections (Hefft and Jonas, 2005), glutamate system dysregulation in schizophrenia (Javitt, 2012) could preferentially target them even in the absence of primary GABAergic disturbances. The issue is also complicated by evidence that at least some PV+ GABAergic synapses may actually be excitatory owing to atypical local chloride gradients at axon initial segments (Woodruff *et al*, 2010). Furthermore, the activity of PV+ cells is modulated by the inhibitory action of nearby CCK+ GABAergic interneurons (Karson *et al*, 2009). Therefore, GAD1 suppression in CCK+ interneurons could actually result in a net increase of inhibitory tone at the circuit level by disinhibiting PV+ cells (Freund and Katona, 2007), suggesting that disturbances in multiple interneuronal sub-populations might have complex, and often unexpected behavioral consequences.

Third, GABAergic dysfunction is not unique to schizophrenia. Nearly all neuropsychiatric disorders include dysfunctional GABA system components: schizophrenia (Hashimoto *et al*, 2008a), bipolar disorder (Fatemi *et al*, 2013; Guidotti *et al*, 2000a), anxiety (Mohler, 2012), depression (Gao *et al*, 2013; Thompson Ray *et al*, 2011), panic disorder (Malizia *et al*, 1998), posttraumatic stress disorder (Geuze *et al*, 2008), attention deficit hyperactivity disorder (Edden *et al*, 2012), autism (Fatemi *et al*, 2010, 2002), Rett syndrome (Blue *et al*, 1999; Chao *et al*, 2010), epilepsy (Kang and Macdonald, 2009), and others (Marin, 2012). There is also some overlap in environmental risk factors such as immune system activation during development in schizophrenia and autism (Michel *et al*, 2012; Patterson, 2009). This raises three intriguing possibilities. First, common insults like MIA might lead to multiple divergent phenotypes depending on the specific timing of the insult during development (Lewis and Levitt, 2002). No where is this potential more evident than in the GABA system where GABA receptor activation has opposite effects on neural activity before and after birth. For example, GABAergic excitation is necessary for DISC1-dependent regulation of neural development (Duan *et al*, 2007;

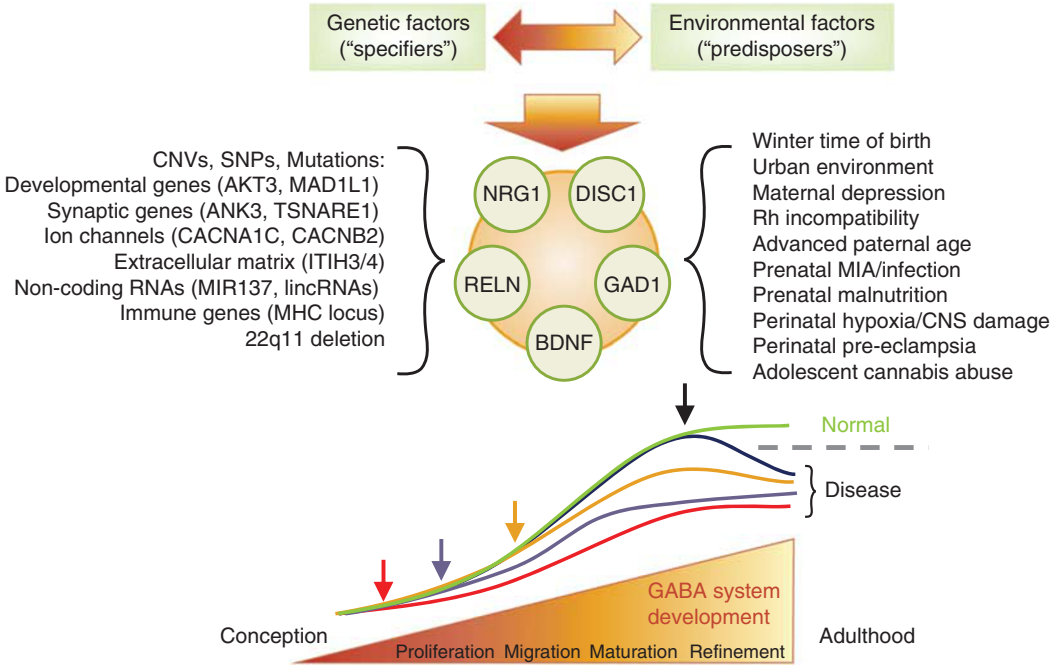

Figure 1. Genetic factors and environmental influences jointly alter normal interneuronal development. Copy number variants (CNVs), single-nucleotide polymorphisms (SNPs), and mutations interact with a host of environmental factors. Their effects summate, and jointly regulate the expression of brain-derived neurotrophic factor (*BDNF*), reelin (*RELN*), neuregulin 1 (*NRG1*), disrupted-in-schizophrenia 1 (*DISC1*) and glutamic acid decarboxylase 1 (*GAD1*). This interaction occurs on a developmental timeline, and alters the typical developmental trajectory of interneurons. Depending on the insults and their timing, the gene × environment (G × E) interaction can disrupt the developmental trajectory at multiple developmental time points (arrows) and might alter cell proliferation, migration, maturation, integration into cortical circuits, or refinement of GABAergic synaptic connections. Such mechanism might explain the variability of GABAergic disturbances seen across the patient cohorts. Regardless of the timing of the insult and the exact time point where the developmental trajectory starts deviating from the typical developmental curve, the end result might be similar—a dysfunctional GABAergic circuitry, which contributes to the emergence of the disease symptoms. Disease threshold is indicated by the dashed gray line. CNS, central nervous system; GABA, gamma-aminobutyric acid; MIA, maternal immune activation.

Kim *et al*, 2012) and NRG1 regulates the expression and activity of GABA receptors and interneuron activity (Li *et al*, 2012; Mitchell *et al*, 2013; Wen *et al*, 2010). Therefore, any environmental exposure affecting *GAD1*, *DISC1*, or *NRG1* might have opposite effects depending on the developmental time point of its introduction. The second possibility is that neuropsychiatric patients are inherently heterogeneous and developmental risk factors common to multiple disorders are found in overlapping parts of the spectrum (Adam, 2013; Insel, 2010). In this context, specific GABAergic deficits reported in multiple disorders may also represent this overlap. This option may be informed by new research initiatives seeking to identify biology underlying specific symptom domains (Cuthbert and Insel, 2013) and subsequent stratification of future clinical studies. A third possible explanation is that environmental factors might predispose to altered trajectory of brain development, but individual genetic susceptibility defines the phenotype (and ultimately the diagnosis). We favor this last explanation (Horvath and Mirnics, 2014b), as MIA and immune system activation predispose to both autism and schizophrenia (Michel *et al*, 2012; Patterson, 2009), and early stress predisposes to a host of psychiatric disorders (Chrousos and Gold, 1992; Corcoran *et al*, 2003; O'Donnell, 2012; Walker *et al*, 2008). However, symptoms of autism emerge very early in life while schizophrenia onset is typically during late adolescence or early adulthood. Therefore, one might argue that the different genetic susceptibilities will define the disease phenotype in a G × E manner, in which the environment can be considered a 'disease-predisposer', and the genetic susceptibility is the 'disease-specifier' (Figure 1). This view has some support from animal studies, where MIA, in conjunction with a schizophrenia-susceptibility genotype (such as *DISC1*), mirrors the late-onset behavioral abnormalities observed in schizophrenia (Abazyan *et al*, 2010; Ibi *et al*, 2010).

Finally, investigation of the pathophysiology of schizophrenia with animal models will remain a major challenge. The mouse brain is different from the human brain and rodents do not get schizophrenia. Furthermore, the utility of animal models in schizophrenia research is limited by the specificity of each hypothesis under examination. Yet, this research will continue to be essential for our understanding of brain function and behavior. Rodent models might not be ideal for determining causal paths to psychosis, but they are extremely valuable when asking well-defined questions about development programs in the brain, the functions of genes, and many other questions. In this context, researchers can assess whether risk factors identified by human genetic and epidemiological studies alter the brain or species-relevant behavior and whether combinations of these risk factors interact as part of larger malfunctioning systems. Taking an 'apples to apples' approach removes confusion associated with attempts to 'diagnose' the behavior of rodents and facilitates fundamental research. In the absence of anthropomorphism, manipulating gene expression in mice has provided a wealth of data regarding the roles *GAD1*, *RELN*, *BDNF*, *NRG1*, *DISC1*, and other genes have in development and behavior. In fact, our understanding of the developmental importance of the GABAergic system comes largely from transgenic mouse research. Simply put, while there are no (and perhaps never will be) 'true' rodent models of schizophrenia or 'schizophrenic mice', a combined use of transgenic technology and environmental challenges in rodent models is essential for understanding genes, cognition, and mental disorders (Brown *et al*, 2013; Garbett *et al*, 2010, 2012; Jaaro-Peled *et al*, 2009; Levitt, 2005; Papaleo *et al*, 2012; Schmidt *et al*, 2013; Schmidt and Mirnics, 2012; Smith *et al*, 2007).

As the field moves toward more complex assessments of the impact of genetic and environmental factors on normal and abnormal brain development, it will be increasingly important to thoughtfully consider and report the precise timing and cell type specificity of the findings. Despite these challenges, we can be hopeful that the wealth of information provided by such studies will identify the biological foundations of specific behavioral dysfunctions. Only then can we build the path to new treatment options, and perhaps arrive to the long-coveted concept of personalized medicine for psychiatric disorders.

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