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Gene-Environment Interactions in Cortical Interneuron Development and Dysfunction: A Review of Preclinical Studies

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Abstract

Cortical interneurons (cINs) are a diverse group of locally projecting neurons essential to the organization and regulation of neural networks. Though they comprise only ~20% of neurons in the neocortex, their dynamic modulation of cortical activity is requisite for normal cognition and underlies multiple aspects of learning and memory. While displaying significant morphological, molecular, and electrophysiological variability, cINs collectively function to maintain the excitatory-inhibitory balance in the cortex by dampening hyperexcitability and synchronizing activity of projection neurons, primarily through use of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Disruption of the excitatory-inhibitory balance is a common pathophysiological feature of multiple seizure and neuropsychiatric disorders, including epilepsy, schizophrenia, and autism. While most studies have focused on genetic disruption of cIN development in these conditions, emerging evidence indicates that cIN development is exquisitely sensitive to teratogenic disruption. Here, we review key aspects of cIN development, including specification, migration, and integration into neural circuits. Additionally, we examine the mechanisms by which prenatal exposure to common chemical and environmental agents disrupt these events in preclinical models. Understanding how genetic and environmental factors interact to disrupt cIN development and function has tremendous potential to advance prevention and treatment of prevalent seizure and neuropsychiatric illnesses.

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Keywords

cortical development; interneuron; developmental neurotoxicity; gene-environment; schizophrenia; seizure

1. Introduction

Disrupted neocortical physiology underlies the neurobehavioral and/or psychiatric pathology associated with a number of common disorders such as epilepsy, schizophrenia, and autism. Though immensely complex, the neocortex is canonically organized along two primary axes: the horizontal laminae and the radial microcircuit columns. Microcircuits, the basic elements of sensory perception and cognition, are composed of functionally entwined excitatory pyramidal neurons and inhibitory interneurons. Pyramidal cells project their axons to distant regions of the cortex or to other parts of the brain and predominantly transmit signals using the neurotransmitter glutamate. Cortical interneurons (cINs), on the other hand, have short, locally connected axons and aspiny to sparsely spiny dendrites. These cells are primarily GABAergic and provide inhibitory input that modulates signal transmission of pyramidal cells^{1,2}. Dysfunction of cINs, which are largely responsible for regulating cortical excitability and synchronizing oscillatory activity, is strongly linked to the development of cognitive and behavioral deficits^{3–6}.

Abnormalities in the neocortical excitatory-inhibitory balance, resulting from cIN defects, are extensively implicated in the pathophysiology of both seizure disorders and neuropsychiatric illnesses^{7–14} (reviewed by Marín et al. and Inan et al.^{15,16}). Increasing evidence supports the idea that cIN abnormalities underlie impairment of complex cognitive tasks, including working memory, sensory integration, and language skills. Though interactions between genetic and environmental influences are suspected to be etiologically culpable in the majority of cases of epilepsy, schizophrenia, and autism, previous examinations have focused primarily on the potential impact of these factors during the postnatal period¹⁷. However, several genetic mutations associated with these diseases disrupt the function of genes involved in cIN development^{18–20}. Additionally, recent studies demonstrate that *in utero* exposure to a number of teratogens, such as alcohol, cigarette smoke, and cannabinoids, disrupts cIN development and results in behavioral abnormalities in animal models^{21–27}. Intriguingly, there is also a growing body of epidemiological data linking human prenatal exposure to these factors to the development of seizure and neuropsychiatric illnesses later in life^{28–30}.

This review examines recent data from preclinical studies that support the emerging link between exposure to common chemical and environmental compounds during critical periods of neurodevelopment and cIN abnormalities associated with complex neuropsychiatric conditions. Though current understanding of cIN development remains incomplete, it is posited that genetic programs controlling cell fate are specified during early embryogenesis and modified by local signals during the post-mitotic maturation period when cINs are migrating and integrating into the cortical circuitry^{31,32}. Elucidating gene-environment interactions that disrupt these complex events should be a priority for

developmental neuroscientists as solving this intricate etiological puzzle could usher in the development of evidence-based prevention strategies and treatments for myriad diseases.

2. Classification of Cortical Interneurons

Consistency in classification is vital for understanding how cINs behave within the neural circuitry and elucidating how their dysfunction may contribute to pathological states. Despite a concerted effort over the past two decades, advancement of a single unifying system has been stymied by the innate heterogeneity and often-overlapping phenotypic range of these cells^{33,34}. The Petilla terminology, proposed by a distinguished group of scholars following an international summit in 2005, improved uniformity of nomenclature used to describe cIN subtypes, but clear groupings remain elusive and classification continues to be primarily descriptive³⁵.

Extrapolating from what is known about interneuronal specification in the spinal cord³⁶, it was initially hypothesized that understanding the developmental origins of cINs would hold the key to defining cardinal classes^{37–39}. Accordingly, a primary focus of the field has been exploring how early specification events drive cIN diversity. While several distinct progenitor niches specified through unique transcriptional cascades have been identified, they do not completely account for the observed biological complexity^{31,40–47}. Additionally, groups of similar cINs within the neocortex and hippocampus have disparate lineages, indicating that different progenitor niches may produce the same subtypes⁴⁸. These observations potentially stem from the presence of highly intricate genetic programs that precisely control cell fate or the remarkable ability of progenitors to respond adaptively to extrinsic influences.

Though no comprehensive classification system yet exists, it is still useful to broadly categorize cINs in terms of neurochemical composition, morphology, and connectivity. Since nearly all cINs express either the calcium-binding protein parvalbumin (PV), the neuropeptide somatostatin (SST), or the ionotropic serotonin receptor 5HT3aR, these markers are frequently used to delineate cINs (listed in Table 1)^{2,49,50}. The PV-expressing cells make up the largest group, accounting for roughly 40% of all cINs. Cells in this group are typically fast spiking and are often divided into two primary populations based on morphology: large basket cells and chandelier cells. Large basket cells tend to synapse at the soma or proximal dendrite of target cells located across multiple layers and are thought to be the dominant source of cortical inhibition^{51,52}. Cells of the SST-expressing group account for about 30% of cINs, are mostly intrinsic burst spiking or accommodating, often target distal dendrites, and can be subdivided into two main groups: Martinotti and small basket cells³. Lastly, the 5HT3aR-expressing group accounts for about 30% of cINs and includes the small bipolar cells that express vasointestinal peptide (VIP) as well as the neurogliaform cells that do not express VIP^{53,54}. Neurogliaform cells are fast-adapting and appear to have a unique place in neural circuits as the only cINs that primarily target other local circuit neurons⁵⁵.

3. Developmental Origins of Cortical Interneurons

Formative work performed by Anderson et al. in 1997 demonstrated that, in contrast to pyramidal neurons which are produced in the dorsal telencephalon, cINs are born within the subpallium and must migrate tangentially to the cortex subsequent to cell cycle exit (schematic in Figure 1 shows migratory routes)⁵⁶. The embryonic subpallium can be divided into five distinct anatomical regions: the medial, lateral, and caudal ganglionic eminences (MGE, LGE, and CGE, respectively), the preoptic area (POA), and the septal anlage. The ganglionic eminences are transient developmental structures that arise from neuroepithelial swellings in the ventral telencephalon around embryonic day 10.5 in the mouse. It was originally suggested that cINs are born within the LGE⁵⁶, but further investigation revealed that the majority actually originate within the MGE and CGE^{40,46,57}, with minority contributions from the LGE and POA^{58,59}. Fate mapping and lineage tracing experiments additionally established that ~60% of cINs, including both PV- and SST-expressing subtypes, are generated within the MGE^{41,57,60} while the 5HT3aR-expressing cells are generated in the CGE⁵³. Generation of cINs occurs primarily between embryonic days 11 and 17 in the mouse, which roughly corresponds to weeks 5 to 15 of pregnancy in humans⁶¹. Although there is some evidence that the generation of cINs in humans does not occur exclusively in the subpallium as it does in rodents⁶², examination of human fetal tissue indicates that the ganglionic eminences are still the primary source of cINs⁶³.

3.1 Fate Determination

Transcriptional networks play an important role in early cIN fate specification (Table 1). The co-repressive morphogens FGF8 and Sonic Hedgehog (SHH) first establish dorsal and ventral domains, respectively, within the forebrain prior to the appearance of the ganglionic eminences. Expression of distal-less homeobox (*Dlx*) transcription factor genes then imparts regional identity to subpallial neural progenitor cells^{20,64,65}. Expression of these genes, especially the functionally redundant members *Dlx1* and *Dlx2*, remains important through later stages of development and is required for tangential migration as well as various aspects of post-mitotic differentiation and maturation, including dendritic arborization^{66–68}. *Nkx2.1*, a homeobox transcription factor-encoding gene, is expressed during early stages of neuroepithelial patterning and is a key regulator of cIN fate. Its expression, which is induced and maintained in the MGE by SHH, is required for the initiation of transcriptional cascades culminating in the specification of both PV- and SST-expressing subtypes^{44,69,70}. Knockout of either *Shh* or *Nkx2.1* in the mouse results in a profound loss of MGE-derived cINs^{71,72}. *Lhx6*, a lim homeodomain transcription factor-encoding gene, is a direct target of NKX2.1 and is necessary for the correct migration and laminar distribution of MGE-derived cINs^{73,74}. Interestingly, reduced *Lhx6* mRNA levels have been reported in patients with schizophrenia⁷⁵. *Sox6* and *Sip1* appear to be important downstream effectors in both cascades as well³⁴. *SatB1* is additionally required for post-mitotic maturation and survival of SST-expressing cells⁷⁶. Though less is known about the transcriptional specification of 5HT3aR-expressing cINs, a recent study demonstrated that expression of *Prox1* and *CoupTF2* within the CGE is necessary⁵⁴. Finally, expression of *Dbx1* in the POA appears to be required for the specification of the small but highly diverse group of cINs generated in this region⁷⁷.

Within the MGE, a number of key spatiotemporal regulators of cIN fate have been identified. The gradient of SHH expression influences the fate of MGE-derived cINs: progenitors exposed to high levels mainly differentiate into SST-expressing cells while those exposed to lower levels mainly differentiate into PV-expressing cells⁷⁸. Additionally, a dorsoventral bias was revealed by explant experiments that demonstrated dorsal MGE tissue predominantly gives rise to SST-expressing cells while ventral MGE tissue predominantly gives rise to PV-expressing cells^{45,47}. A recent study also showed that SST-expressing cINs are preferentially derived from apical progenitors within the ventricular zone of the MGE while PV-expressing cINs are preferentially derived from basal progenitors within the subventricular zone of the MGE⁷⁹. Lastly, evidence from birthdating analyses suggests that there is a bias for production of SST-expressing cINs during the early neurogenic period and PV-expressing cINs during the late neurogenic period⁴³. Currently, though, the potential impact of environmental disruption on these early specification events is poorly understood.

3.2 Migration and Integration

Following cell cycle exit, cIN precursors migrate tangentially to the dorsal telencephalon and align along both sides of the developing cortical plate before undergoing radial migration and integration into neural circuits. Analogous to the radial migration of pyramidal cells, this requires permissive substrates, modulation of cell adhesion molecules, and intricate combinations of chemoattractive and chemorepulsive factors⁸⁰. Both Slit-Robo and Eph-Ephrin signaling have been implicated in the initial guidance of cINs away from the subpallial proliferative zones^{81,82}. Hepatocyte growth factor/scatter factor (HGF/SF), brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), and neurotrophin 4 (NT4) function as key motogens which drive migrating cINs toward the pallium^{83–86}. Once cINs have reached the developing cortical plate, neuregulin1-ErbB4 and stromal-derived factor 1 (SDF-1)-Cxrc4 signaling appear to play an important role in regulating cIN integration^{87,88}. Lastly, upregulation of the potassium-chloride co-transporter KCC2 mediates the excitatory to inhibitory change in GABAergic signaling⁸⁹. This switch, which begins late in gestation and continues into the postnatal period, is sufficient to suppress cIN motility and marks the initiation of terminal differentiation and circuit refinement, a stage during which cINs adopt mature expression profiles and connective characteristics.

To better understand the function of cINs within neural networks and how their dysfunction may contribute to disease, an increasing effort has been made in recent years to understand how cINs are integrated into the neocortical circuitry. Similar to pyramidal neurons, the laminar fate of MGE-derived cINs correlates strongly with birthdate^{40,41}. Generation of these neurons occurs in an “inside-out” fashion with earlier born cells occupying the deep cortical layers and later born cells filling in the more superficial layers. In contrast, the ultimate location of CGE-derived cINs appears to be more heavily dependent on radial sorting mechanisms^{90–92}. Despite the fact that these cells initiate migration and entry into the cortical plate concurrently to age-matched MGE-derived cINs, their final destination cannot be predicted by birthdate.

Recent advances in clonal labeling techniques have allowed for more sophisticated analyses of the distribution of cIN lineages through the cortex. Though this process appears to be stochastic, evidence suggests that cells sharing a common lineage are targeted to specific cortical areas⁹³. Additionally, individual neuronal precursor cells have the capacity to give rise to phenotypically divergent mature cINs⁹⁴. Thus, functional interactions with local excitatory neurons are thought to play an important role in the final postmigratory differentiation of cINs^{34,95}. Furthermore, cINs exhibit remarkable functional plasticity and molecular expressivity in response to external stimuli⁹⁶. Together these findings indicate that cIN fate is far more flexible than originally suspected and is not exclusively predetermined by developmental origin but rather can be modified by the local milieu or extrinsic environmental factors during the postmitotic period.

4. Disruption of Cortical Interneuron Development

Defects in early cIN development can have a variety of significant anatomical and physiological effects. Genetic mutations and/or exposure to teratogens during critical periods of brain development have the capacity to alter the total number of cINs produced, disrupt tangential migration patterns, and/or cause subtype misspecification errors with a variety of functional manifestations. Consequences can range from severe, debilitating neurological disability to subtler impairments in learning and social behavior. Critically, abnormal cIN development is implicated in the pathogenesis of a number of common seizure and neuropsychiatric disorders, including epilepsy, schizophrenia, and autism. However, the intrinsic and extrinsic factors capable of disrupting cIN development, and the potential synergistic interactions between these factors, are not yet completely understood.

Despite extensive efforts to elucidate the genetic basis of diseases such as epilepsy, schizophrenia, and autism, a limited number of definitive associations have been uncovered. Though large genome-wide association studies have been undertaken, no single mutation has been identified that adequately predicts risk of the above diseases in large populations (for further discussion of the genetic basis of these diseases see Myers et al., Farrell et al., and Muhle et al.^{97–99}). Of the genetic variants implicated in these disorders, the vast majority appear to act with low penetrance and broad phenotypic expressivity, features indicative of significant etiological complexity. For example, 22q11.2 deletion syndrome (OMIM #188400), which results in an abnormal distribution of PV-expressing cINs, has been identified as the cause of schizophrenia in ~1% of cases^{100,101}. However, only about 25% of mutation carriers meet the criteria for diagnosis of schizophrenia¹⁰². Further, examination of twin concordance for epilepsy, schizophrenia, and autism indicate that, as with other complex diseases, it is highly likely that the etiology of these disorders is multifactorial^{103–108}. Exemplifying this concept, abnormal cIN development and schizophrenia-like behavioral pathology in dominant-negative DISC1 mice is exacerbated by neonatal immune activation¹⁰⁹. This finding highlights the need for careful exploration of how relevant environmental agents augment risk of disease in genetically predisposed individuals. As such, there has recently been an increased effort to understand how naturally occurring compounds, environmentally significant chemical hazards, and illicit/pharmaceutical drugs impact cIN development. Within the past 5 years, more than a dozen reports have been published that directly and mechanistically link these factors to

perturbation of key cIN developmental events in animal models (see Figure 2). Here, we focus our discussion on the molecular outcomes associated with prenatal exposure to four common human teratogens: ethanol, cigarette smoke, and illicit and prescription drugs.

4.1 Cortical Interneurons as a Teratogenic Target

4.1.1 Prenatal Ethanol Exposure—Though the devastating effects of maternal alcohol consumption on the developing fetus were first documented over a century ago, it is estimated that roughly 1 in 10 pregnant women in the US still uses alcohol during pregnancy^{110,111}. Prenatal ethanol exposure causes a range of structural and functional abnormalities, collectively termed fetal alcohol spectrum disorder (FASD). At the severe end of this spectrum is fetal alcohol syndrome (FAS), marked by growth retardation, a specific pattern of craniofacial dysmorphology, and CNS dysfunction (relevant neurobehavioral and clinical aspects of FASD/FAS have been recently reviewed by Coriale et al.¹¹²). Multiple characteristics of FAS and FASD in patient cohorts are consistent with a cIN-mediated excitatory-inhibitory imbalance including heightened risk of seizures and epilepsy, and impaired executive functioning¹¹³. In mice, prenatal alcohol exposures that cause the classic facial features of full-blown FAS also result in a marked deficiency of the MGE, a reduced number of cIN precursors, and abnormal cIN tangential migration patterns^{114–116}. Such exposures significantly reduce the total number of cINs and alter the subtype balance in the postnatal brain²⁷. In addition, early binge-type prenatal exposure has been linked to an abnormal distribution of PV-expressing cINs in the medial prefrontal cortex¹¹⁷. This interneuropathy persists into adulthood and is marked by significant electrophysiological and behavioral alterations in affected mice¹¹⁸.

The type and severity of CNS abnormalities resulting from prenatal ethanol exposure, however, appear to depend upon variables beyond the level of exposure itself^{119,120}. Animal models show that the impact of alcohol exposure on the developing embryo is shaped by both the timing of exposure as well as interacting genetic variations^{121–124}. These studies also highlight the interaction of ethanol with SHH signaling by demonstrating that mutations in multiple pathway members increase the severity of ethanol-induced abnormalities. In fact, ethanol appears to act, at least in part, by directly antagonizing the SHH signaling pathway^{125–127}. Although multiple mechanisms of action have been proposed, ethanol-mediated disruption of SHH signal transduction serves as a unifying basis for the classic features of FAS and FASD, including facial dysmorphology, and cIN abnormalities. Interestingly, this pathway is also inhibited by a number of dietary and environmental chemicals, including compounds found in tomatoes, potatoes, and insecticide formulations^{128,129}. The relationship between prenatal exposure to these compounds and cIN pathology, however, has not yet been investigated.

4.1.2 Cigarette Smoking—Though maternal cigarette smoking during pregnancy has been slowly declining over the past few decades, self-reporting indicates that more than 10% of women in the US continue to smoke through the gestational period¹³⁰. Maternal cigarette smoking during pregnancy is associated with numerous poor outcomes including fetal growth restriction, spontaneous abortion, preterm birth, and increased risk of sudden infant death²⁹. Additionally, epidemiological studies strongly link maternal cigarette smoking

during pregnancy to the diagnosis of psychobehavioral pathology during childhood and adolescence^{28,131–135}. These studies show that children born to mothers that smoke during pregnancy are at increased risk of developing neuropsychiatric conditions such as attention deficit hyperactivity disorder and conduct disorder. Though the biological basis of this is not yet fully understood, prenatal nicotine exposure may have a direct effect on cINs in developing neural networks. Activation of nicotinic acetylcholine receptors on human cINs can trigger post-synaptic release of GABA¹³⁶. Though it is plausible that inappropriate activation of developing cINs may disrupt circuit dynamics and impair formation of networks, there is currently insufficient evidence to support this conclusion.

Intriguingly, an alternative explanation for the link between maternal smoking and the development of psychobehavioral disorders has recently been advanced. In the mouse, prenatal exposure to carbon monoxide, which models aspects of the effects of maternal cigarette smoking, downregulates signaling through cGMP and its target vasodilator-stimulated phosphoprotein, leading to disrupted actin polymerization in developing neurons, reduced migratory capacity, and abnormal laminar distribution of cINs, but not excitatory neurons, in the adult brain²³. Furthermore, these effects were correlated with the development of abnormal sensory-related behaviors in mice.

Since cigarette smoke is a cocktail composed of thousands of chemicals, maternal smoking may alter numerous aspects of cIN development. As this is explored in greater depth, it is likely that additional mechanistic explanations for the link between smoking during pregnancy and the development of complex neuropsychiatric disorders will begin to emerge. Moving forward, it will be important to remain cognizant of the potential for gene-environment interactions and to examine how individual genetic susceptibility may influence the degree to which these cIN disruptions affect neurobehavioral function.

4.1.3 Illicit and Prescription Drug Use—Associating illicit and prescription drug use during pregnancy with specific teratogenic outcomes is difficult as multiple substances may be used together and self-reporting is often inaccurate. Additionally, a single substance may have variable effects depending on dose and timing of exposure while different substances can have similar, overlapping effects. A 2012 survey indicated that about 5% of pregnant women had used an illicit substance within the past month¹³⁷. A conservative extrapolation suggests more than 200,000 babies in the US are exposed to illicit drugs *in utero* each year. This staggering statistic speaks the importance of understanding both the structural and functional effects such substances may have on developing neural systems.

Though women of childbearing age may attempt to reduce substance use during pregnancy, confirmation of pregnancy often comes after critical windows of neurodevelopment have passed. Cannabis (marijuana) is one of the most widely used illicit substances and prenatal exposure is linked to a number of poor neurobehavioral outcomes¹³⁸. Endogenous cannabinoid signaling is thought to play a role in prenatal neurodevelopment and cannabinoid receptors are expressed in the cranial neural plate and prosencephalic neuroepithelium during periods of early forebrain patterning¹³⁹. 9-tetrahydrocannabinol (THC), the psychoactive component of cannabis, effectively crosses the placenta and *in utero* exposure reduces the number of hippocampal interneurons produced and alters social

behavior in mice²⁵. Though the effects of THC on cIN development specifically are not known, prenatal exposure to synthetic cannabinoids during the period of neurulation profoundly disrupts cortical development in mice. Observed defects following treatment with the synthetic cannabinoid CP-55,940 range from cortical dysplasia to holoprosencephaly (incomplete medial forebrain division). Holoprosencephaly is marked by a deficiency of ventral midline tissue and co-occurs with a significant loss of SST-expressing cINs in humans¹⁴⁰. This suggests that prenatal cannabis exposure, especially during the first trimester of pregnancy, has the potential to significantly perturb cIN development.

While less is known about how other drugs may impact developing cINs, there is sufficient evidence suggesting this is an area that deserves greater attention. Methamphetamine, a potent neurotoxin, selectively causes apoptosis of PV-positive, but not SST-positive, striatal interneurons¹⁴¹. Its effects on cINs and developing neuronal populations, though, have not yet been examined. Prenatal phencyclidine (PCP) exposure reduces the density of PV-expressing cINs and disrupts the formation of prefrontal cortical circuits leading to behavioral deficits in mice¹⁴². Intriguingly, prenatal cocaine exposure, which is thought to primarily target dopaminergic and serotonergic systems, impairs tangential migration and causes a reduction of both the total number of cINs and the percentage of PV-expressing cINs in the medial prefrontal cortex of adult mice^{143,144}. The epidemiological significance of *in utero* methamphetamine, PCP, and cocaine exposures, however, is unknown.

Prescription drugs may also disrupt cIN development. Maternal use of valproic acid (VPA), a prescription anticonvulsant and mood stabilizer, during pregnancy has been strongly correlated with an increased risk of autism in the child^{145,146}. Not surprisingly, exposure around the third week of pregnancy, the onset of neurulation, is reported to have the most devastating effects. In a rat model, prenatal VPA exposure results in hyperconnectivity of cortical microcircuits and a subsequent loss of signal integration, suggesting that function of cINs may be impaired¹⁴⁷. Though the cellular and molecular effects of antidepressants are not yet completely understood, emerging evidence suggests that developing cINs may be susceptible to modulation by these drugs. Chronic administration of the selective serotonin reuptake inhibitor fluoxetine leads to structural changes in cINs and a reduction of PV-expressing cINs in the medial prefrontal cortex of adult mice^{148,149}. The effects of fluoxetine on developing cINs, however, have not been examined despite evidence that the drug effectively crosses the placenta and leads to the development of anxiety-like behavior in prenatally exposed rats^{150,151}. Clearly, further investigation into the effects of illicit and prescription drugs on the development of cINs is needed for accurate risk assessment and hazard communication.

4.1.4 Non-Chemical Factors—In addition to chemical insults, other extrinsic factors can alter cIN development. Complications during pregnancy are a known risk factor for the development of schizophrenia¹⁵². Though this link was previously thought to be a result of fetal hypoxia, recent studies demonstrated that in the mouse, prenatal stress impairs cIN migration, increases the total number of cINs present during critical periods of adolescence, delays maturation of PV-expressing cells, and alters social behavior^{24,153}. Intriguingly, prenatal stress also leads to epigenetic modification of cINs and the development of schizophrenia-like behavioral features in mice¹⁵⁴. In neonatal rats, exposure to bouts of

intermittent hypoxia, which models hypoxia-related obstetric complications or severe respiratory disease, decreases PV-expressing cINs in the prefrontal cortex and increases anxiety-like behavior later in life¹⁵⁵. A similar deficit of PV-expressing cINs was found in a model of maternal immune activation during pregnancy²⁶, an established risk factor for the development of schizophrenia and autism in patient cohorts^{156–158}. Lastly, fetal infections, which potentially lead to a loss of cIN progenitors, have also been linked to the development of schizophrenia later in life¹⁵⁹. Notably, prenatal Zika virus infection was recently correlated with increased apoptosis of cIN progenitors¹⁶⁰. How any of these factors potentially augment genetic predisposition, though, remains to be elucidated.

5. Future Directions

Previous efforts have focused heavily on understanding the genetics of common seizure and neuropsychiatric illnesses. However, it is quickly becoming evident that genetics alone cannot explain occurrence of these common conditions and detection of environmental factors that lead to cIN dysfunction is of utmost importance. The above examples constitute an important proof of principle that cIN development is exquisitely sensitive to teratogenic disruption, but the list is far from comprehensive. It is impractical to depend solely on epidemiological investigations and animal trials to uncover other operational environmental factors. Additionally, reliance on these methods limits ability to concurrently test interacting genetic susceptibilities. Thus, new approaches to screen for environmental factors that disrupt cIN development and to model gene-environment interactions must be developed.

Though etiological and biological complexity has long frustrated advancement of such tools, the technology and resources to do this are now becoming available to researchers^{161–163}. Breakthroughs in cIN culture techniques, such as the ability to produce differentiated cINs from human embryonic and induced pluripotent stem cells, should spur development of *in vitro* testing models that not only replicate key biological complexities but are also genetically tractable and amenable to high throughput chemical screening^{164,165}. As part of a concerted toxicology forecasting effort (ToxCast), the EPA assembled a small molecule library of over 1,800 chemicals with a broad range of structures from diverse sources including industrial and consumer products, food additives, and potentially “green” chemicals that could be safer alternatives to existing chemicals. Using this library to screen cultured cINs for defects in proliferation, differentiation, migration, and neurite outgrowth should uncover novel environmental hazards that may contribute to the etiology of diseases stemming from disruptions in cIN development. Additionally, use of CRISPR/Cas9 technology will enable modeling of known and discovered individual and familial genetic variants and allow for higher throughput analysis of potential gene-environment interactions.

6. Conclusion

The “two-hit” hypothesis states that when a disease cannot be clearly linked to a single genetic predisposition or relevant environmental agent, its etiology is likely multifactorial. In such cases, genetic predisposition may alter individual sensitivity to environmental influences. In recent years, a great number of genetic variants and teratogens have been identified that alter cIN development. However, as neither genetic susceptibility nor

environmental exposure alone can accurately predict risk of developing epilepsy, schizophrenia, or autism, the pathology associated with these diseases likely results from intricate interactions between both elements. How environmental factors superimposed with genetic susceptibility contribute to the pathogenesis of seizure disorders and neuropsychiatric illnesses, though, remains to be determined. In addition, the capability of neural circuits to adapt to developmental insults and the mechanisms by which they may do so are not yet understood. Exploring these complex avenues will undoubtedly advance design of effective preventative strategies for a number of common, debilitating conditions. Furthermore, technical advances fueled by understanding of cIN development are quickly making cell culture and grafting therapies imaginable treatments for these devastating disorders^{166,167}.

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Highlights

- This review explores the emerging link between common teratogens and abnormal cIN Development
- cIN dysfunction is associated with multiple common seizure and neuropsychiatric disorders
- Understanding culpable etiological factors will advance treatment and prevention of these diseases

Figure 1. Cortical Interneuron Development

Upper left: Three-dimensional reconstruction of the brain and face of a fetal mouse derived from high resolution magnetic resonance microscopy sections. The light green square indicates plane of section for the schematic illustration to the right. *Right:* Schematic illustration of the developing telencephalon at approximately embryonic day 15. Dark green arrows indicate possible routes of cortical interneuron (cIN) tangential migration from the subpallial proliferative zones to the cortex. cINs born during the early neurogenic period primarily enter the cortex via a superficial stream within the marginal zone (1,3), while those that are born during the late neurogenic period enter via a deeper stream into the intermediate and subventricular zones (2). Subsequent to tangential migration, cINs align along either side of the cortical plate before undergoing radial migration and integration. LGE, MGE, CGE: lateral, medial, and caudal ganglionic eminences. POA: preoptic area.

Figure 2. Cortical Interneuron Development is Highly Sensitive to Teratogenic Disruption

Left: Timeline of critical periods in human and mouse cortical interneuron (cIN) ontogenesis. *Right:* Common teratogens target key events in cIN development including initial fate specification, proliferation, tangential migration from the subpallium to the cortex, circuit integration, and adoption of mature expression and connective profiles. Highlighting the emergent nature of the field, 68% (n=15/22) of the studies supporting this list were published within the past 5 years. Asterisks (*) denote areas where further experimental evidence is required to substantiate the association. dpc: days post conception, E: embryonic day, PD: postnatal day.

Table 1
Classification of Cortical Interneurons

Cortical interneurons (cINs) are grouped into primary classes based on presence of three markers that are expressed by nearly 100% of cINs: parvalbumin (PV), somatostatin (SST), and the 5HT3aR serotonin receptor. The vast majority of cINs are born within the medial and caudal ganglionic eminences (MGE and CGE, respectively). Cell fate is determined, at least in part, through the combinatorial expression of region-specific transcription factors. Subclasses are highly diverse in terms of morphology, biochemical composition, and electrophysiological profile.

Marker	Fate Specification	Birthplace	% of Total	Subclasses
PV	<i>Dlx1/2, Nkx2.1, Lhx6, Sox6, Sip1</i>	MGE	~40%	Large basket, Chandelier
SST	<i>Dlx1/2, Nkx2.1, Lhx6, Sox6, Sip1, SatB1</i>	MGE	~30%	Martinotti, Small basket
5HT3aR	<i>Dlx1/2, Prox1, CoupTF2</i>	CGE	~30%	Neurogliaform, Small Bipolar