Published in final edited form as:

Neuroimage. 2019 January 15; 185: 802–812. doi:10.1016/j.neuroimage.2018.04.032.

A Review on Neuroimaging Studies of Genetic and Environmental Influences on Early Brain Development

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Abstract

The past decades witnessed a surge of interest in neuroimaging study of normal and abnormal early brain development. Structural and functional studies of normal early brain development revealed massive structural maturation as well as sequential, coordinated, and hierarchical emergence of functional networks during the infancy period, providing a great foundation for the investigation of abnormal early brain development mechanisms. Indeed, studies of altered brain development associated with either genetic or environmental risks emerged and thrived. In this paper, we will review selected studies of genetic and environmental risks that have been relatively more extensively investigated-familial risks, candidate risk genes, and genome-wide association studies (GWAS) on the genetic side; maternal mood disorders and prenatal drug exposures on the environmental side. Emerging studies on environment-gene interactions will also be reviewed. Our goal was not to perform an exhaustive review of all studies in the field but to leverage some representative ones to summarize the current state, point out potential limitations, and elicit discussions on important future directions.

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Keywords

Early brain development; MRI; Infancy; Risk Genes; Prenatal drug exposure; Maternal Disorders; gene-environment interactions

INTRODUCTION

Complex interactions between genes and environment during development determine the structural and functional growth of the brain and behavior. Directly linking particular genetic and environmental risk factors to specific behaviors has proven to be extremely challenging due to the lack of one-to-one links. Notably, numerous studies on neurodevelopmental and/or psychiatric brain disorders confirm that a disorder is usually associated with a variety of genetic and/or environmental risk factors (Abrahams and Geschwind, 2008; Walsh et al., 2008) while a known genetic and/or environmental risk may result in different variants of behavioral phenotypes (Hessl et al., 2001; Hoffbuhr et al., 2002; Warren and Li, 2005; Yehuda et al., 2006). Part of the reasons for this lack of specificity arises from the fact that neither genes nor the environment directly code for/influence behavior but work together to determine the building blocks of different cells in the brain, the collective effort of which ultimately produces behavior. Therefore, brain measures represent a critical intermediate step between risk factors and behavioral output and have the potential to reveal more specific mechanisms since brain-related phenotypes (e.g., volume, cortical thickness, white matter diffusivity, and functional connectivity, etc.) can be determined for specific regions, networks, and systems, most of which can be more objectively quantified than behavioral phenotypes (Gao et al., 2016; Graham et al., 2014; Raschle et al., 2012). Together with the advancement of various neuroimaging techniques, many studies have turned to brain measures as a stepping stone to bridge the gap between genes/environment and behavior (Lenroot and Giedd, 2008).

Existing studies of gene-brain and environment-brain relationships in the adult brain shed lights on different risk factors that are likely associated with different brain disorders (Caspi and Moffitt, 2006; Chiang et al., 2009; Glahn et al., 2010; Thompson et al., 2001). However, these relationships reflect a long history of convolved interactions between genes/environment and the brain that spans across a prolonged period of postnatal development. Therefore, the translational value is limited since it is extremely challenging, if at all possible, to reverse the long-accumulated effects through medical, behavioral, or other interventions. Together with the increasing consensus that most, if not all, brain disorders have developmental origins (Insel, 2010; O'Donnell and Meaney, 2017; Swanson and Wadhwa, 2008), focus has been increasingly shifted to the identification of genetic and/or environmental risk factors that affect early brain development. Particularly, studies during the neonatal/infancy period have the best potential to minimize postnatal influences that could potentially mask early impacts. Therefore, such studies tend to offer a better depiction of genetic/environmental influences on early brain development. Moreover, this early window hosts one of the most active phase of brain development when many of the brain's structural, functional, and behavioral processes are unfolding, thus the early impacts are likely amplified with age. The idea that small disturbances during early development spread

over time to produce large deviations from typical growth trajectories has been largely agreed on and gone by many names including developmental cascades, chain reactions, and butterfly, snowball, amplification, spillover, or progressive effects (Masten and Cicchetti, 2010). Therefore, the study of pre- and perinatal risks during early infancy period represents a priority from both scientific and clinical perspectives (Gao et al., 2016; Masten and Cicchetti, 2010).

Given the relatively limited behavioral repertoire and practical difficulties associated with infant behavioral evaluation, studying the brain directly is of particular importance. However, accurate delineation of effects of risks in the infant brain has previously been limited by technical difficulties on non-invasive imaging with high spatial fidelity. Basically, electroencephalogram (EEG) (Anderson et al., 1985; Dreyfus-Brisac and Larroche, 1971; Videman et al., 2016; Wen et al., 2017b) and functional near-infrared spectroscopy (fNIRS) (Grossmann and Johnson, 2010; Nakano et al., 2009; Wilcox et al., 2010; Wilcox et al., 2012) represent some of the most widely applied techniques to explore infant brain development. However, their poor spatial resolution (centimeters) and low depth penetration (limited to cortical regions) make them less ideal tools to examine potentially subtle and region-specific effects. In contrast, non-invasive magnetic resonance imaging (MRI) represents a versatile tool that is known to have high spatial resolution (millimeters), provide whole brain coverage, and be able to explore both the structural and functional aspects of infant brain development (Cao et al., 2017; Deoni et al., 2011; Gao et al., 2009a; Gilmore et al., 2007; Gilmore et al., 2012; Hazlett et al., 2017; Huang et al., 2015; Huang et al., 2006). However, due to low tolerance to movement artifacts, most MRI studies of the infant brain are conducted during either natural (Gao et al., 2016; Gao et al., 2009b) or sedation-induced sleeping state(Allievi et al., 2016; Arichi et al., 2012). The sleeping state likely would not affect structural brain examinations but investigations of active functional responses requiring awake state is largely prohibited. Fortunately, recent advancements in resting-state fMRI technique (Biswal et al., 1995) that is capable of delineating the brain's intrinsic functional architecture in sleeping infants opened a promising new window to peek into functional alterations in the infant brain associated with different genetic and/or environmental risks (Doria et al., 2011; Fransson et al., 2007; Gao et al., 2014; Gao et al., 2016; Gao et al., 2009b; Smyser et al., 2010).

Admittedly, neuroimaging study of gene-/environment-brain relationships during infancy is itself in its infancy. In this preliminary review, we sought to summarize findings from the first set of such studies to better understand the current state of the field, point out potential limitations, and elicit discussions on future directions. We will focus on selected categories of genetic and environmental risk studies that have been relatively more extensively investigated. Specifically, we will cover familial risks, candidate risk genes, and genome-wide association studies (GWAS) on the genetic side and maternal mood disorders and prenatal drug exposures on the environmental side. Studies on potential gene-environment interaction mechanisms will also be touched upon. We fully appreciate that there are other categories of risks (e.g., poverty, maternal obesity, pollution, etc.) and variants of studies but they are beyond the scope of this review. This review is organized as follows: in section 1 we describe the potential mechanisms and experimental findings on the effects of genetic risks on early brain development; in section 2, we introduce the potential mechanisms and

experimental findings on the effects of maternal mood disorders and prenatal drug exposures on early brain development; in section 3, we will discuss potential gene-environment interaction effects on early brain development; in section 4 we briefly summarizes the practical considerations in neonatal neuroimaging; finally, we point out some limitations of current studies and discuss future directions moving forward. The selectively discussed neuroimaging studies of genetic and environmental influences on early brain development in this review are listed in Table 1.

1. Neuroimaging study on the effects of genetic risks on early brain development

Although single-gene disorders can produce complex behavioral phenotypes as in Rett syndrome, Lesch–Nyhan Syndrome, and Fragile X, modern genetic research indicates that common behavioral conditions such as autism and attention-deficit-hyperactivity disorder reflect the action of multiple genes acting in concert with non-genetic factors (Goldstein and Reynolds, 2011). While potential mechanisms and preliminary studies of gene-environment interactions will be discussed in section 3, this section will focus on studies that specifically examine genetic risks without substantial consideration of environmental variables.

Expression of disease-related genes during pre- and perinatal development— Precise regulation of gene expression has been well documented in human brain development. Importantly, it has been shown that 90 per cent of genes expressed in the brain are differentially regulated both spatially and temporally and the bulk of this spatio-temporal regulation occurred during prenatal development (Kang et al., 2011). For example, for *DCX*, a gene expressed in neuronal progenitor cells and immature migrating neurons, its expression increases until early mid-fetal development and then gradually declines, consistent with the growth of immature neurons. In contrast, genes expressed in dendrites (*MAP1A, MAPT, CAMK2A*) and synapses (*SYP, SYPL1, SYPL2, SYN1*) show steep increases between the late mid-fetal period and one year of postnatal age, in line with the documented growth trajectories of dendritic arborization and synaptogenesis (Tau and Peterson, 2010). Notably, many genes associated with autism spectrum disorder (ASD), schizophrenia, and intellectual disability also exhibit elevated expression in fetal and early postnatal life (Birnbaum et al., 2015; Birnbaum et al., 2014). Specific examples include CNTNAP2, which encodes a neurexin family protein implicated in ASD and is highly enriched in orbital and dorsal lateral prefrontal cortices during fetal development while its expression increases in other cortical areas during early infancy, and NRGN, a gene encoding a postsynaptic protein kinase substrate associated with schizophrenia which is highly expressed in all cortical areas starting from birth and continuously increases in expression until late childhood (Kang et al., 2011). The documented high level of expression of disease-related genes during pre- and perinatal development suggests that the fetal and neonatal brain may be particularly susceptible to risk-related genetic variation. Indeed, emerging neuroimaging studies of infant brain development have provided solid evidence for this hypothesis. These includes studies of infants at high familial risk for psychiatric disorders, candidate gene studies, and genome-wide association studies.

Studies of infants at high familial risk for psychiatric disorders—Regarding high familial risk, the majority of work in this area has focused on infant siblings of children with

autism(Hazlett et al., 2017; Lewis et al., 2017; Shen et al., 2017; Wolff et al., 2015). Because autism can be diagnosed as early as two-years of age, these studies also allow comparisons between high-genetic risk individuals who progress to an autism diagnosis and those who do not. These studies indicate that children who go on to a diagnosis of ASD are distinguished by atypical longitudinal brain changes, from 6–24 months of age. In particular, these infants exhibit a greater increase in brain volume from 12–24 months of age (Hazlett et al., 2017), increased surface area expansion from 6 to 12 months of age (Hazlett et al., 2017), an increase in size of the genu of the corpus callosum at 6 month of age, followed by a declining growth trajectory (Wolff et al., 2015), and expanding regions of decreased efficiency (weighted distance between two nodes using number and distance of white matter fiber tracts) beginning in the right temporal lobe at 6 months and expanding to temporal, parietal and occipital lobes by 24 months (Lewis et al., 2017). These children also show increased extra-axial cerebral spinal fluid (CSF) volume at 6 months of age (Shen et al., 2017). A study of genetic risk for schizophrenia (i.e., maternal diagnosis of schizophrenia or schizoaffective disorder)(Gilmore et al., 2010) found that male neonates at genetic risk for schizophrenia had larger intracranial, total gray matter, and CSF volumes than control neonates. In a follow-up study from the same group, Shi et al (Shi et al., 2012) went on to show that male neonates at genetic risk for schizophrenia also demonstrated lower efficiency, less hubs, and longer connection distance according to graph theory-based analysis of morphological brain networks. A preliminary study (Li et al., 2016) of cortical thickness and surface area, also be the same group, suggested that the widespread cortical thinning observed in adults with schizophrenia was not present in neonates, but region-specific alterations are detectable. Notably, male and female at-risk neonates showed very different profiles in comparison to typical controls (Li et al., 2016).

Studies of candidate genes—The first candidate gene study of infant neuroimaging phenotypes was carried out by Knickmeyer et al (Knickmeyer et al., 2014). In this study of ~1 month old infants, carriers of the apolipoprotein E (APOE) ε4 variant, a major susceptibility factor for late onset Alzheimer's disease (AD), had reduced gray matter volume in medial temporal cortex, suggesting the ε4 variant's contribution to brain phenotypes associated with Alzheimer's risk is present before birth. Brain volume differences were also observed for other risk genes, including disrupted-in-schizophrenia-1 (*DISC1*), catechol-O-methyltransferase (*COMT*), neuregulin (*NRG*), brain-derived neurotrophic factor (*BDNF*), and glutamate decarboxylase 1 (*GAD1*) (Knickmeyer et al., 2014). Consistent with these findings, BDNF polymorphism has recently been shown to be associated with individual differences in temperament in 4-month-old infants (Giusti et al., 2017). A subsequent study of healthy infant (2~25 months of age) carriers and non-carriers of the APOE ε4 allele observed lower white matter myelin water fraction and gray matter volume in infant ε4 carriers (Dean et al., 2014) in precuneus, posterior/middle cingulate, lateral temporal, and medial occipitotemporal regions, areas preferentially affected by AD. Finally, a recent study by Krishnan et al (Krishnan et al., 2017) has reported that common genetic variation in *DLG4* (rs17203281) is associated with fractional anisotropy in preterm infants. In addition to being required for synaptic plasticity associated with NMDA receptor signaling, *DLG4* is a hub protein in the microglial inflammatory response. The authors

hypothesize that this particular genetic variant may modulate responses to neuroinflammation in children born preterm (Krishnan et al., 2017).

Although fascinating, these results must be considered in light of known pitfalls and limitations of candidate gene studies. First, candidate gene studies only investigate a few a-priori variants of interest; these genes likely represent a very small fraction of all variants involved in human brain development. Second, sample sizes are relatively modest (272 for Knickmeyer et al. 2014; 162 for Dean et al. 2014; and 70 and 271 (2 cohorts) for Krishnan et al., 2017). They are thus well powered to detect large and moderate effects sizes, but would be underpowered to detect genetic effects typical for genome-wide association studies (GWAS) of human disease (Collins et al., 2012). It was originally hoped that effect sizes for brain phenotypes would be larger than those for psychiatric disease itself, but recent GWAS of global and subcortical brain volumes in adults suggest this might not be the case (Hibar et al., 2017; Stein et al., 2012). Third, as in all areas of science, replication is critical for delineating between true-positive and false-positive effects. Most of the variants studied in Knickmeyer et al. (2014) have not been evaluated in independent neonate samples. There is some overlap between Knickmeyer et al. (2014) and Dean et al. (2014) in terms of brain areas effected by APOE ε4. Krishnan et al. (2017) investigated two cohorts; significant effects of *DLG4* (rs17203281) were observed in both. Finally, it should be noted that, with the exception of APOE, genes investigated in Knickmeyer et al (2014) have not emerged as significant psychiatric risk genes in subsequent GWAS studies. While they clearly play important roles in brain development, they may not be directly relevant to mental health.

Genome-wide association studies (GWAS)—For all the above-mentioned reasons, focus has increasingly shifted from candidate gene approaches to genome-wide association studies (GWAS). The first GWAS on structural brain development in a population cohort of infants (Xia et al., 2017) revealed an intronic single-nucleotide polymorphism (SNP) in *IGFBP7* (rs114518130) which achieved genome-wide significance for gray matter volume and an intronic SNP in *WWOX* (rs10514437) which neared genome-wide significance for white matter volume. The former locus is also within 100kb of *REST*, a master negative regular of neurogenesis which binds at thousands of locations across the genome (Johnson et al. 2007). Additional loci with small p-values tagged psychiatric GWAS associations, transcription factors expressed in developing brain, and other genes with strong biological plausibility including *HTR1B*, which encodes the 5-hydroxytryptamine (serotonin) receptor 1B, and *RBFOX1*, an RNA splicing factor which regulates expression of large genetic networks during early neuronal development. Krishnan et al (2016) have also used genome wide data to assess whether common genetic variation influenced white matter microstructure in preterm infants. As they had a very small sample size (72 infants), they focused on pathway and network-based approaches. Results suggest a possible role for peroxisome proliferator-activated receptor signaling (Krishnan et al., 2016). These early results suggest that GWAS studies of infant neuroimaging phenotypes will be fruitful in terms of identifying genes and molecular pathways involved in prenatal and infant brain development. However, GWAS studies come with their own methodological pitfalls and limitations. These have been reviewed in detail elsewhere (Karlsen et al., 2010; Riancho, 2012), but we will highlight three issues in particular here. First, GWAS is most effective

when traits are underpinned by a small number of loci with large effect sizes. Most human traits examined thus far do not follow this pattern; instead they are underpinned by many loci with small effect sizes. GWAS requires thousands or tens of thousands of individuals to detect these effects. Such sample sizes are not yet available for infant neuroimaging phenotypes. Second, the large number of statistical tests performed in a GWAS study means that a high number of associations arise by chance. Even with stringent thresholds, replication is key. This has not yet been possible for infant neuroimaging studies, due to the lack of multiple, large cohorts with GWAS genotypes. This situation is likely to change in the near future as infant neuroimaging becomes more common and independent groups start working together as in the ENIGMA (Enhancing Neuro Imaging Genetics through Meta-Analysis) consortium (Bearden and Thompson, 2017). Finally, spurious associations may arise due to technical or complex genetic reasons (such as population stratification: the presence of a systematic difference in allele frequencies between subpopulations in a population due to different ancestry). Replication will be important for ruling out such effects.

Overall, these studies corroborate the rich gene expression during pre-/perinatal development and indicate that brain alterations associated with different risk genes can be detected during early infancy. Further investigations are needed to explore the potential to develop robust imaging-based biomarkers for later onset of behavioral problems and/or disorders among infants at risk. Promising results have emerged from studies of infants at high genetic risk for autism where cortical surface features and resting-state connectivity measured in the first year of life distinguish children who go on to develop autism from those who do not (Emerson et al., 2017; Hazlett et al., 2017). However, as most cases of autism (and other serious mental illnesses) are sporadic, similar studies in population cohorts are urgently needed.

2. Neuroimaging study on the effects of environmental risks on early brain development

Environmental factors have been shown to exert vital effects on early brain development(Booij et al., 2015; Thompson et al., 2009). Similar as section 1, while its interactions with genes are robustly documented and will be discussed later, this section will focus on studies of environmental risks including maternal mental disorders and prenatal drug exposures, without substantial consideration of genetic variants.

Environmental risk factors for mental disorders are diverse in nature but could be categorized in three main categories based on timing: 1) prenatal risks, including maternal mood disorders (e.g., depression/anxiety), substance abuse (e.g., prenatal drug exposure) during pregnancy, among others; 2) perinatal risks, including low birth weight, birth complications, and deprivation of normal parental care during early infancy, among others; 3) risks in childhood and beyond, including childhood abuse, childhood neglect, premature parental loss, exposure to family conflict and violence, trauma, substance abuse, and toxic exposure, among others. In this review, we will highlight selected studies of the first two categories of risks.

Studies of prenatal maternal mood disorders—Prenatal maternal mood disorders are associated with an increased risk for neurobehavioral, cognitive/socio-emotional problems (Waters et al., 2014), and depression in the offspring (Field et al., 2004; Pawlby et al., 2009; Pearson et al., 2013). Although the precise mechanisms underlying the effects of maternal mood status on fetal development remains to be determined, evidences accumulate on alterations in hormones and neurotransmitters in the uterine environment (Van den Bergh et al., 2005). For example, studies have shown that levels of cortisol are highly correlated between paired maternal and fetal plasma samples (Gitau et al., 1998). Moreover, newborns of prenatally depressed mothers exhibit biochemical profiles similar to those observed in depressed mothers, including elevated cortisol and norepinephrine and lower dopamine and serotonin (Field et al., 2004). Notably, proper functioning of these hormones and neurotransmitters is critical for the timing and guidance of neurogenesis, neuronal differentiation/migration, apoptosis, synaptogenesis and myelination (Nowakowski and Hayes, 2002). Therefore, disturbances of the delicate balance between these hormones and neurotransmitters in the fetus related to maternal depression would likely influence critical prenatal programing of different neural circuits thus shedding far reaching effects on offspring behavior. Of particular importance are the potential impacts on the hypothalamic–pituitary–adrenal (HPA) axis (Challis et al., 2001), the limbic system, and the prefrontal cortex, which may collectively contribute to cognitive/emotional regulation problems of children born to mothers with mood disorders.

Neuroimaging studies of effects of prenatal maternal mood disorders are emerging. In one study of maternal anxiety, Qiu et al (Qiu et al., 2013) reported that children of mothers with elevated anxiety levels showed slower growth of bilateral hippocampal volume during the first six months of life. Moreover, the left and right hippocampal growths show differential reactivity to postnatal maternal anxiety levels. Maternal anxiety in pregnancy was also associated with variation in fractional anisotropy (FA) of brain regions important to cognitive-emotional responses to stress (i.e., the right insula and dorsolateral prefrontal cortex), sensory processing (e.g., right middle occipital), and socio-emotional function (e.g., the right angular gyrus, uncinate fasciculus, posterior cingulate, and parahippocampus), which in turn predicted infant internalizing but not externalizing behavior 1 year later (Rifkin-Graboi et al., 2015). The same group also reported reduced water diffusivity and fractional anisotropy properties of the right amygdala in neonates born with mothers with higher depressive symptoms (Rifkin-Graboi et al., 2013) and altered functional connectivity patterns of the amygdala in 6-month-old infants born from mothers with greater maternal depressive symptoms (Qiu et al., 2015a). A follow-up study in 4.5-year-old children(Wen et al., 2017a) shows that greater prenatal maternal depressive symptoms were associated with larger right amygdala volume in girls, but not in boys. Likewise, postnatal maternal depression promotes forms of parenting (Fleming et al., 1988) that enhance stress reactivity, social withdrawal, and inattention (Bruder-Costello et al., 2007; Degnan et al., 2010; Moffitt et al., 1996), which in turn predicts an increased risk for depression and behavioral problems in the offspring (Mars et al., 2015; Matijasevich et al., 2015). Increased postnatal maternal depressive symptoms were associated with higher right amygdala FA in the overall sample and girls, but not in boys (Wen et al., 2017a). Interestingly, in a general population, the infant spent at least 50% of his/her day time hours with his/her mother, both lower maternal

sensitivity and higher maternal depression predicted greater relative right frontal EEG asymmetry (Wen et al., 2017b). Furthermore, greater relative right frontal EEG asymmetry of 6-month-old infants predicted their greater negative emotionality at 12 months of age. This suggested that amongst infants with sufficient postnatal maternal exposure, both maternal sensitivity and mental health, are important influences on early brain development (Wen et al., 2017b). These studies provide compelling evidence that maternal mood disorders, both prenatal and postnatal, could affect in-utero and/or postnatal brain development, especially within limbic structures involved in arousal and emotion regulation, presenting some initial clues on the brain mechanisms of transgenerational transmission of vulnerability for mood disorders during pre- and postnatal development.

Studies of prenatal drug exposures—Prenatal drug exposures comprise another category of environmental risk that has received considerable research interest in recent years(Behnke et al., 2013; Brady et al., 2003; Chasnoff et al., 1986; Ching and Tang, 1986; Derauf et al., 2009), partly due to the alarming rate of increase in substance abuse during pregnancy (Behnke et al., 2013; Ross et al., 2015). Prenatal drug exposure affects fetal brain development both directly (most drugs readily cross both the placenta(Behnke and Eyler, 1993) and blood-brain-barriers(Schou et al., 1977) to bind with endogenous receptors in fetal brain during critical periods) and indirectly through actions on the placenta (Bhide and Kosofsky, 2009). In fetal brain, different drugs act via shared and unique pathways but the most important ones relate to the disruptions of endogenous neurotransmitter systems which play important roles in brain development during critical periods of gestation(Nowakowski and Hayes, 2002). For example, the primary psychoactive compound in marijuana, Δ^9-tetrahydrocannabinol (THC), is an exogenous cannabinoid which binds to type 1 cannabinoid receptors. This likely disrupts endogenous cannabinoid signaling which plays a critical role in control of neurogenesis, phenotypic specification of immature neurons, and establishment of the normal fetal neuronal network architecture (Gaffuri et al., 2012; Harkany et al., 2008). On the other hand, prenatal cocaine and amphetamines act primarily within the mesolimbic dopaminergic pathway to increase volume and duration of monoamines (dopamine, serotonin, norepinephrine) within the synapse. Opioid mechanisms may include altered fetal brain opioid receptor (OR) expression, opioid-linked decreases in myelin volume and maturation(Eschenroeder et al., 2012; Sanchez et al., 2008; Vestal-Laborde et al., 2014), and enhanced activity of locus coeruleus neurons (Aghajanian et al., 1992; Duman et al., 1988; Nestler et al., 1994, 1999; Selley et al., 1997; Van Bockstaele et al., 2010; Van Bockstaele and Valentino, 2013) that would naturally restrain noradrenergic activation throughout the brain which may then contribute to greater stress reactivity and arousal(Kinney et al., 1990). Opioid-related epigenetic effects include hypermethylation to silence not only (mu)OR, but also global DNA expression(Doehring et al., 2013; Knothe et al., 2016). Moreover, interactions between OR gene variants and epigenetic effects may yield differential responses to similar exposures(Oertel et al., 2012).

In human children and adolescents, prenatal drug exposures are linked to abnormal brain volumes(Dow-Edwards et al., 2006), impaired white matter microstructures(Derauf et al., 2009; Warner et al., 2006), and different cognitive/behavioral deficits (Connor et al., 2006; Leech et al., 1999; Walhovd et al., 2007; Walhovd et al., 2010). While studies in children

and older populations may be confounded by postnatal influences, emerging neuroimaging studies in the neonatal brain provide initial confirmation of the prenatal effects of drug exposure. Specifically, Grewen et al (Grewen et al., 2014) conducted one of the first MRI studies of effects of prenatal drug exposures on neonatal structural brain development. They reported reduced prefrontal and frontal gray matter volume and enhanced whole brain CSF volumes in neonates with prenatal cocaine exposure (PCE, comorbid with other drugs) compared with drug-free newborns and those with exposure to similar other drugs but not cocaine, indicating PCE-specific effects on structural brain growth are evident in neonates. Subsequently, Salzwedel et al (Salzwedel et al., 2016; Salzwedel et al., 2015) published the first studies on the effects of PCE on neonatal functional brain development using resting-state fMRI. They reported aberrant amygdala-prefrontal (Salzwedel et al., 2015) and thalamus-frontal (Salzwedel et al., 2016) functional connectivity specifically associated with PCE. Drug-common alterations in thalamus-motor area connectivity were also observed (Salzwedel et al., 2016). In addition to cocaine, the same group also examined effects of prenatal marijuana exposure on neonatal functional brain organization and reported reductions in connectivity of insula and striatal seeds with multiple visual and cerebellar regions (Grewen et al., 2015). In another study of prenatal exposure to antiepileptic drugs using EEG, Videman et al (Videman et al., 2016) showed significant differences in several features of neonatal cortical electrical activity, including alpha bursts, frequency spectrum, and spatial distribution of bilateral synchrony. King et al., also reported disruption of auditory gating measured by EEG in 4–6 month old infants exposed to prenatal nicotine (King et al., 2017). Importantly, Salzwedel et al (Salzwedel et al., 2016) went on to show that degrees of functional connectivity disruption in neonates associated with prenatal drug exposure significantly predicted cognitive and motor-related outcome measures at 3 months of age. Although preliminary and requiring independent validation, these findings provide exciting new directions in the search of imaging-based biomarkers for later behavioral outcomes in these at-risk infants. Another important issue/limitation of drug exposure research relates to the fact that drug-using mothers rarely use a single drug so it's difficult to tease out drug-specific effects. That being said, the potential drug-drug interaction effects are also critical research questions. Indeed, a preliminary examination of the potential interaction effects between cocaine and selective-serotonin-reuptake-inhibitor (SSRI) (Salzwedel et al., 2016) indicated that the combined use of both cocaine and SSRI during pregnancy resulted in the worst outcomes on thalamocortical functional connectivity, highlighting the necessity of further research on this important topic. Overall, existing studies provide convergent evidence on the effects of prenatal drug exposure on neonatal brain structural and functional development but important limitations associated with multi-drug usage has to be better addressed in future studies.

3. Interactions between genetic risks, prenatal drug exposures, and other family environment factors

Long debates between nature and nurture have gradually converged on the idea that they both have vital influences on brain and behavioral development while most, if not all, parts of their influences are unfolded in a time-dependent manner through complex interactions rather than single-domain actions. This hypothesis implies that individual differences in genetic makeup will modulate individual differences in their resilience or vulnerability to

environmental adversities and vice versa- individual differences in environmental exposures may modulate subject-specific gene expression along time (i.e., epigenetics). This gene-environment bi-directional conversation was observed in cases of both early adverse life events and prenatal drug exposure. For example, Caspi et al (Caspi et al., 2002) reported that a functional polymorphism of the gene encoding the neurotransmitter-metabolizing enzyme monoamine oxidyase A (MAOA) moderated the effect of childhood maltreatment in violence behaviors. For prenatal drug exposure, both animal models (Downing et al., 2009; Goodlett et al., 1989) and human studies (Jacobson et al., 2006; Streissguth and Dehaene, 1993) have convincingly demonstrated that genetic background can confer either susceptibility or resilience to risks of prenatal drug exposure (Goodlett et al., 1989). From the other direction, the effects of early life adversities have been well studied and findings suggest that early life adverse exposures can disrupt gene expressions not only in specific candidate genes but also on the whole genome at both brain and peripheral level (Bick et al., 2012). Similarly, different fetal drug exposures were shown to alter gene expression in the brain in both animal and human studies (Gangisetty et al., 2014; Lester and Padbury, 2009; Lussier et al., 2015).

While relatively extensive gene-environment interaction studies have been conducted during childhood and beyond as mentioned above, little was done to characterize such interactions during early brain development, especially those using brain measures as the target phenotype. Among the few existing studies, Qiu et al (Qiu et al., 2015b) showed that individual COMT SNPs modulated the association between antenatal maternal anxiety and the prefrontal and parietal cortical thickness in neonates. Specifically, the A-val-G (AGG) haplotype probabilities modulated positive associations of antenatal maternal anxiety with cortical thickness in the right ventrolateral prefrontal cortex and the right superior parietal cortex and precuneus. In contrast, the G-met-A (GAA) haplotype probabilities modulated negative associations of antenatal maternal anxiety with cortical thickness in bilateral precentral gyrus and the dorsolateral prefrontal cortex. In another study of maternal depression (Qiu et al., 2017), the same group found that a genomic profile risk score for major depressive disorder (GPRSMDD) moderated the association between antenatal maternal depressive symptoms and the right amygdala volume in neonates, further underscoring the gene-environment interdependence in fetal brain development. The study also identified that glutamate receptor activity played an important role in the relationship between prenatal maternal depressive symptoms and neonatal right amygdala volume. Multiple approaches, including genome-wide analyses, implicate glutamatergic synaptic transmission in the etiology of depression (Lee et al., 2012; Skolnick et al., 2009) and patients with major depressive disorder (MDD) exhibit abnormal glutamate concentrations in the amygdala (Michael et al., 2003). Post-mortem studies with MDD suggest altered glutamatergic synaptic signaling (Hashimoto et al., 2007) and ketamine, a glutamatergic intervention, is a treatment for MDD (Caddy et al., 2014). Interestingly, the direction of the interaction between maternal depressive symptoms and infant genotype on right amygdala volume in the US sample is in the opposite direction to that observed in the Asian sample, suggesting that despite common underlying biological processes, polymorphisms may operate in an ethnicity-specific manner(Qiu et al., 2017). Taken together, encouraging preliminary results on the gene-environment interaction effects on early brain development

have emerged but more systematic studies and independent validations are desperately needed to further our understanding of this complex issue.

4. Practical considerations in neonatal/infant imaging

In clinical settings, neuroimaging of infants are routinely conducted during sedation but for ethical considerations, sedation is not an option for most developmental neuroimaging research. In contrast, imaging naturally sleeping infants represents the most common practice in developmental neuroimaging studies (Gao et al., 2016). Many challenges exist for the preparation and actual imaging of non-sedated, naturally sleeping infants and certain procedures have been developed to cope with such challenges (Raschle et al., 2012). First, careful preparation and proper environment should be given to help caregivers to put the infant to sleep. Examples include scheduling the session during the infant's nap time, pre-exposure to the scanner noise through a CD for at least a week before appointment, feeding and swaddling in a dimmed room before imaging (or inside the scanner room), and reserving at least a two-hour time slot to accommodate sleep preparation time, among others. To prepare for actual imaging after the infant fall asleep, proper ear protection (e.g., ear plugs, noise-cancelling headphones) must be in place, the infant need to be wrapped and secured on the scanner bed (preferably with a warm blanket on top of a secured mattress), and proper monitoring devices for vital signals (e.g., heart rate, blood pressure, and pulse oximetry) are connected, for imaging. During image acquisition, besides the caregiver, a pediatric nurse should stay in the imaging suite to monitor the vital signals for safety. If the infant begins to wake, MRI acquisition can be paused and the caregiver can try to soothe the infant back to sleep. However, if the infant cries or becomes distressed, the scan needs to be stopped and the infant be removed from the scanner. For a more detailed discussion on the challenges, procedures, and ethical considerations related to infant neuroimaging, please refer to (Raschle et al., 2012).

Conclusions, Limitations and Future Directions—Overall, the field of early brain development witnessed a surge of interest in characterizing the effects of genetic and environmental risks using different neuroimaging techniques during the past decades. In this review, we have summarized findings from selected studies on familial risks for psychiatric disorders, candidate gene studies, and GWAS studies on the genetic side; and maternal mood disorders and prenatal drug exposures on the environmental side. Moreover, preliminary studies on the gene-environment interactions in infants are also discussed. Overall, as summarized above, existing studies have consistently conveyed the idea that structural and functional brain alterations associated with both genetic and environmental risks, as well as their interactions, could be detected as early as in neonates. Moreover, the abnormality profiles may change with age and differ between boys and girls. By further linking early brain alterations to behavioral outcomes, these studies provide the exciting first set of evidences demonstrating the potential of neuroimaging in the early identification of risks for later development problems and/or disorders.

As encouraging as these previous studies are, the field is likely still in its infancy. As partly mentioned above in separate sections, there are many issues calling for more future studies to address. For example, most studies of infants at high familial risk (Gilmore et al., 2010;

Hazlett et al., 2017; Li et al., 2016; Wolff et al., 2015) have not integrated neuroimaging with molecular genetics, so the specific genes and pathways underlying the observed associations are unclear. Although machine learning-based approaches (Hazlett et al., 2017) show promising classification results but these findings need to be validated in independent samples. For candidate gene studies, known risk genes represent a very small fraction of all variants involved in the development of human brain. Furthermore, many of the 'classic' candidate genes in psychiatry (with the exception of the APOE ε4 allele) have not been supported by recent large-scale GWAS studies. For GWAS studies, sample size is a major limiting factor so large-scale collaborations as exemplified by ENIGMA (Bearden and Thompson, 2017) are needed in the infant population to overcome this barrier. For studies of maternal mood disorders, active medication use represents a confounding factor and should be better controlled in future studies. For prenatal drug exposure studies, multiple drug usage acts as a major limitation for characterization of brain changes associated with a specific drug. Future studies simultaneously modeling all drugs, as well as their interactions, are needed to tease our drug-specific effects but much larger sample sizes are likely needed to offer enough power for such multivariate estimation. Overall, for both genetic and environmental risk studies, it is critical to consider the other part of the equation and emphasize their interactive effects on early brain and behavioral development. Better understandings of the mechanisms leading to adverse developmental outcomes can only be achieved through combined examination of both the genetic makeup and environmental exposures since each of the two domains of factors can offer either protection against or catalyst for the expression of the effects from the other domain. However, the issue of sample size becomes even more challenging in these studies so multi-sites collaborations are critical in future attempts of systematic delineation of gene-environment interaction effects on early brain and behavioral development. Therefore, it is essential that the field can embrace the open-science concept and move forward through more data sharing and closer collaboration.

In the future, two of the most important and overarching questions deserve the whole field to rally around and tackle. The first question is "What do the observed early brain alterations tell us about future behavior"? Answering this question requires not only early imaging during infancy but also longitudinal follow-up of behavioral outcomes. More importantly, successful prediction would have to rely on the development of advanced analytical algorithms capable of handling the multimodal, large-scale neuroimaging features, including the increasingly popular deep-learning and artificial intelligence techniques. Encouraging preliminary predictions have been reported (Emerson et al., 2017; Hazlett et al., 2017; Rifkin-Graboi et al., 2015; Salzwedel et al., 2016) but much more efforts are needed to build and independently test different prediction models to achieve the goal of deriving imaging-based biomarkers for early identification of risks. The second question is "What can we do to modify the aberrant brain growth thus improving behavioral outcomes"? Existing studies already provided clues on the environmental and/or genetic risk factors that affect early brain development but much more work need to be done for these findings to guide meaningful interventions (e.g., environmental modification, behavioral therapy, medication, or new generation gene editing techniques). Examples include the establishment and independent validation of causal pathways of action, development of new behavioral/

environmental/genetic intervention strategies, and deriving image-based quantitative biomarkers to gauge the effects of intervention trials, among others. Apparently, answers to these two questions represent some of the most important long-term goals in the developmental research field and many challenges need to be overcome before their advent. Importantly, such a monumental endeavor requires collective efforts from different fields including but not limited to imaging, developmental psychology, genetics, neuroscience, and advanced computation. Therefore, interdisciplinary collaboration is a must in the long journey from imaging to imaging-based prediction and intervention design, the advent of which, hopefully, could provide desperately needed help to the affected children and their families.

Acknowledgments

This work is supported by the National Institutes of Health: NS088975 to WG, DA042988, DA043171, and DA036645 to WG and KG, MH070890 and HD053000 to JHG, MH092335 and MH104330 to RKS, U01MH110274 (UNC/UMN Baby Connectome Project) to WL, and by National Medical Research Council: NMRC/TCR/012-NUHS/2014 to AQ.

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Table 1

List of selected neuroimaging studies of genetic and environmental influences on early brain development discussed in this review.

1. Studies of infants at high familial risk for psychiatric disorders			
Article	**Population**	**N**	**Main Findings**
Gilmore et al., 2010	Neonatal offspring of mothers with schizophrenia or schizoaffective disorder and matched comparison mothers without psychiatric illness	26 offspring of mothers with schizophrenia or schizoaffective disorder and 26 matched controls	The high-risk neonates had non-significantly larger intracranial, cerebral spinal fluid (CSF), and lateral ventricle volumes. Subgroup analysis revealed that male high-risk infants had significantly larger intracranial, CSF, total gray matter, and lateral ventricle volumes; the female high-risk neonates were similar to the female comparison subjects.
Shi et al., 2012	Same as Gilmore et al., 2010	Same as Gilmore et al., 2010	The brain structural associations of the high-risk neonates tended to have globally lower efficiency, longer connection distance, and less number of hub nodes and edges with relatively higher betweenness. Subgroup analysis showed that male neonates were significantly disease-affected, while the female neonates were not.
Li et al., 2016	Same as Gilmore et al., 2010	21 offspring of mothers with schizophrenia or schizoaffective disorder and 26 matched controls	Female high-genetic-risk neonates had significantly thinner cortical thickness in the right lateral occipital cortex than the female control neonates. High-genetic-risk neonates had marginally different cortical thickness in a number of other brain areas.
Wolf et al., 2015	Infants at high risk for autism spectrum disorder (ASD, having an older sibling with a community diagnosis of ASD) and control groups.	270 infants at high familial risk for ASD and 108 low-risk controls at 6, 12 and 24 months of age	Significantly increased corpus callosum area and thickness in children with ASD starting at 6 months of age followed by a declining in growth rate, resulting diminished differences at 2 years of age.
Shen et al., 2017	Same as Wolf et al., 2015	221 infants at high risk for ASD and 122 low risk controls at 6, 12 and 24 months of age	Infants who developed ASD had significantly greater extra-axial CSF volume at 6 months compared with comparison groups
Lewis et al., 2017	Same as Wolf et al., 2015	260 infants at 6 and 12 months of age with our without known risk for ASD	Inefficiencies in high-risk infants later classified as ASD were detected from 6 months onward in regions involved in low-level sensory processing.
Hazlett et al., 2017	Same as Wolf et al., 2015	106 infants at high familial risk of ASD and 42 low-risk infants	Hyperexpansion of the cortical surface area between 6 and 12 months of age precedes brain volume overgrowth observed between 12 and 24 months in 15 high-risk infants who were diagnosed with autism at 24 months. Brain surface area information of 6–12-month-old individuals predicted the diagnosis of autism in individual high-risk children at 24 months.
Emerson et al., 2017	Same as Wolf et al., 2015	59 6-month-old infants with a high familial risk for ASD	Functional connectivity magnetic resonance imaging features measured at 6 months of age correctly identified which individual children would receive a research clinical best-estimate diagnosis of ASD at 24 months of age.
2. Studies of candidate genes			
Knickmeyer et al., 2014	Neonates with or without parental psychiatric history.	272 neonates.	Local variation in gray matter volume was significantly associated with polymorphisms in DISC1 (rs821616), COMT, NRG1, APOE, ESR1 (rs9340799), and BDNF. Neonates homozygous for the DISC1 (rs821616) serine allele exhibited reduced GM in the frontal lobes, and neonates homozygous for the COMT valine allele exhibited reduced GM in the temporal cortex and hippocampus.
Dean et al., 2014	Healthy, typically developing 2- to 25-month-old infants with no family history of Alzheimer disease or other	162 infants at 2–25 months of age.	Infant apolipoprotein E (APOE) ε4 allele carriers had lower myelin water fraction (MWF) and gray matter volume (GMV) measurements than non-carriers in areas preferentially affected by AD. They also showed

Article	Population	N	Main Findings
	neurological or psychiatric disorders		greater MWF and GMV measurements in extensive frontal regions.
Krishnan et al., 2017	Preterm infants	Two independent cohorts of preterm infants (cohort 1: n = 70; cohort 2: n = 271)	Common genetic variation in *DLG4* (rs17203281) is associated with fractional anisotropy in preterm infants
3. Genome-wide association studies (GWAS)			
Xia et al., 2017	Infants (300 male, 261 female) between 0 and 24 weeks of age, including 295 singletons or unpaired twins, 17 sibling pairs and 232 twins.	561 infants	An intronic single-nucleotide polymorphism (SNP) in IGFBP7 (rs114518130) achieved genome-wide significance for gray matter volume (P=4.15 × 10–10). An intronic SNP in WWOX (rs10514437) neared genome-wide significance for white matter volume (P=1.56 × 10–8).
Krishnan et al., 2016	Preterm infants (mean gestational age (GA) 28 + 4 weeks, mean postmenstrual age (PMA) at scan 40 + 3 weeks)	72 preterm infants.	Significant relationships between lipid pathways, peroxisome proliferator-activated receptor (PPAR) signaling particularly, and variability in preterm white matter development, measured by fractional anisotropy were detected. Five genes were found to be highly associated with the phenotype: aquaporin 7 (AQP7), malic enzyme 1, NADP(+)-dependent, cytosolic (ME1), perilipin 1 (PLIN1), solute carrier family 27 (fatty acid transporter), member 1 (SLC27A1), and acetyl-CoA acyltransferase 1 (ACAA1).
4. Studies of prenatal maternal mood disorders			
Qiu et al., 2013	Full term infants	175 neonates with 35 of them having repeated MRI scans at 6 months	Children of mothers reporting increased anxiety during pregnancy showed slower growth of both the left and right hippocampus over the first 6 months of life.
Qiu et al., 2015a	Full term infants	24 infants at 6 months of age	Infants born to mothers with higher prenatal maternal depressive symptoms showed greater functional connectivity of the amygdala with the left temporal cortex and insula, as well as the bilateral anterior cingulate, medial orbitofrontal and ventromedial prefrontal cortices.
Rifkin-Graboi et al., 2013	Full term neonates	157 neonates	Significantly lower fractional anisotropy and axial diffusivity, but not volume, were detected in the right amygdala in the infants of mothers with high compared with those with low depression scores.
Wen et al., 2017a	4.5-year-old children	235 children	Greater prenatal maternal depressive symptoms were associated with larger right amygdala volume in girls, but not in boys. Increased postnatal maternal depressive symptoms were associated with higher right amygdala FA in the overall sample and girls, but not in boys.
5. **Studies of prenatal drug exposures**			
Grewen et al., 2014	Full term neonates with or without prenatal drug exposure	33 with PCE co-morbid with other drugs, 46 drug-free controls and 40 with prenatal exposure to other drugs (nicotine, alcohol, marijuana, opiates, SSRIs) but without cocaine.	Reduced prefrontal and frontal gray matter volume and enhanced whole brain CSF volumes in neonates with prenatal cocaine exposure (PCE) compared with drug-free newborns and those with exposure to similar other drugs but not cocaine.
Salzwedel et al., 2015	Same as Grewen et al., 2014	Same as Grewen et al., 2014	Drug-common effects were detected within the amygdala–frontal, insula–frontal, and insula–sensorimotor circuits. A prenatal cocaine exposure (PCE)-specific effect was detected within a sub-region of the amygdala–frontal network.
Grewen et al., 2015	Same as Grewen et al., 2014	20 with prenatal marijuana exposure (PME) co-morbid with other drugs, 20 drug-free controls and 20 with prenatal	Both marijuana-specific and drug-common alterations in functional connectivity were detected among a range of functional circuits associated with the

1. Studies of infants at high familial risk for psychiatric disorders			
Article	**Population**	**N**	**Main Findings**
		exposure to other drugs (nicotine, alcohol, marijuana, opiates, SSRIs) but without marijuana.	amygdala, hippocampus, putamen, anterior/posterior insula, caudate, and anterior/posterior thalamus.
Salzwedel et al., 2016	Same as Grewen et al., 2014	Same as Grewen et al., 2014	PCE-related hyper-connectivity between the thalamus and frontal regions and a drug-common hypo-connective signature between the thalamus and motor-related regions were detected. PCE-specific neonatal thalamo-frontal connectivity was inversely related to cognitive and fine motor scores and thalamo-motor connectivity showed a positive relationship with composite motor scores. Moreover, cocaine by selective-serotonin-reuptake-inhibitor (SSRI) interactions were detected, suggesting the combined use of these drugs during pregnancy could have additional consequences on fetal development.
6. Studies of interactions between environmental and genetic effects			
Qiu et al., 2015b	Same as Qiu et al., 2013	146 neonates	Individual COMT SNPs modulated the association between antenatal maternal anxiety and the prefrontal and parietal cortical thickness in neonates. Specifically, the A-val-G (AGG) haplotype probabilities modulated positive associations of antenatal maternal anxiety with cortical thickness in the right ventrolateral prefrontal cortex and the right superior parietal cortex and precuneus.
Qiu et al., 2017	Same as Qiu et al 2013	168 and 85 mother–infant dyads from Asian and United States of America cohorts, respectively	A genomic profile risk score for major depressive disorder (GPRSMDD) moderated the association between antenatal maternal depressive symptoms and the right amygdala volume in neonates.