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Review

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# Epigenetic Regulation of Infant Neurobehavioral Outcomes

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## Key Words

Neurobehavior · Epigenetics · Neonatal Intensive Care Unit Network Neurobehavioral Scales · Placenta · Autism · DNA methylation

## Abstract

During fetal development and early infancy, environmental signals can induce epigenetic changes that alter neurobehavioral development and later-life mental health. Several neurodevelopmental genetic diseases influence epigenetic regulatory genes and genomic imprinting. Recently, brain epigenetic marks have been involved in idiopathic neurodevelopmental disorders, including autism spectrum disorders. The placenta is an important regulator of the intrauterine environment that links maternal and fetal nervous systems. Placental epigenetic signatures have been associated with the neurodevelopment of healthy newborns quantified through the Neonatal Intensive Care Unit Network Neurobehavioral Scales (NNS). Associations have been observed for DNA methylation of genes involved in cortisol (*NR3C1*, *HSD11B*), serotonin (*HTR2A*), and metabolic (*LEP*) pathways. Dysregulation of imprinted genes and microRNAs has also been associated with neurobehavior assessed by NNS. Further analysis is needed to characterize the mechanisms by which the epigenome influences neurodevelopment and the connection between this dysregulation and mental health disorders. In the future, epigenetic marks could serve as functional biomarkers of mental health and cognitive function.

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## Introduction

The developmental origins of health and disease hypothesis proposes that environmental cues during fetal development and early infancy induce adaptive responses that can influence later-life disease susceptibility [1]. Populations exposed to prenatal famine show an increased risk of later-life mental outcomes, specifically schizophrenia, depression, addiction and dysregulation of stress response, suggesting that intrauterine conditions program later-life mental health [2]. This early-life programming requires plasticity, thus epigenetic mechanisms have been proposed as molecular mediators because these integrate genetic and environmental signals with the control of gene expression [3].

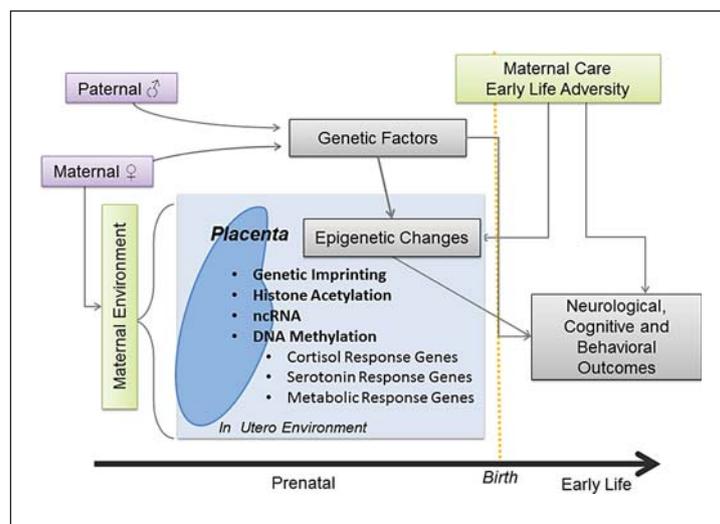
Epigenetics is the study of heritable but feasibly environmentally modifiable control of gene expression potential without DNA sequence changes [4]. The major systems of epigenetic regulation include DNA methylation, genomic imprinting, non-coding RNAs and histone modifications. DNA methylation is the best-characterized epigenetic mark and involves the addition of a methyl group to cytosines usually within CpG dinucleotides that in promoters frequently results in gene silencing [4]. Epigenetic regulation is essential during development when somatic and germ cells experience a global epigenetic remodeling that regulates cell and tissue differentiation [5, 6]. The quality of the environment during this and other sensitive periods could alter this epigenetic reprogramming. Rodent studies have shown that maternal behavior in early life influences offspring behavior during adulthood through epigenetic deregulation of *NR3C1* and other loci [7–9]. This suggests that during intrauterine and early postnatal life, epigenetic programming occurs that has long-term influences on mental health (fig. 1).

In this review, we outline the evidence relating epigenetic variation and neurodevelopmental diseases and discuss epigenetic marks in the placenta, a crucial organ for intrauterine development, and their role in infant neurodevelopmental outcomes.

## Role of Epigenetics in Neurodevelopmental Disease

The significance of epigenetics in neurodevelopment is illustrated in genetic conditions that influence epigenetic regulatory genes and affect cognitive functions [10]. Rett syndrome is a neurodevelopmental condition associated with autism spectrum disorder (ASD), and is

**Fig. 1.** Diagram of principal factors influencing infant neurobehavior. Maternal and paternal genetics influence neurological, cognitive and behavioral outcomes. The in utero and early-life environment can also influence these outcomes through epigenetic mechanisms. The placenta regulates the in utero environment, and its epigenetic profiles can contribute to infant neurobehavior.



caused by genetic mutations in the X-linked *MECP2* [11]. MeCP2 is a chromatin-associated protein that binds to methylated DNA, is highly expressed in the brain and is required for neuronal maturation. Loss or aberrant MeCP2 function leads to epigenetic deregulation and impaired synaptic function [10, 12]. Similarly, genomic imprinting disorders of 15q11–13 lead to Angelman syndrome and Prader-Willi syndrome, neurodevelopmental pathologies with structural and functional brain changes [13–15]. Imprinted genes are expressed in a parent-of-origin-specific manner because DNA methylation silences the other allele [16]. A large proportion of imprinted genes are expressed in the brain, and imprinting disorders frequently exhibit neurodevelopmental delay [13]. Although most Angelman syndrome and Prader-Willi syndrome cases are caused by genetic changes, in some cases, loss of gene function is attributable to an imprinting defect or epimutation [17]. Moreover, 15q11–13 duplications are frequent cytogenetic abnormalities in ASD [18].

The majority of neurodevelopmental disorders, including ASD, cannot be directly associated with specific genetic changes, but have complex genetic and environmental influences contributing to disease [18]. Since epigenetic mechanisms integrate these signals, a number of studies suggest that idiopathic neurodevelopmental disorders may result from epigenetic dysregulation of neurological pathways. Most human studies of neurobehavioral disease and epigenetics (table 1) [19–27] compare epigenetic profiles between ASD cases and controls in post mortem brain samples, a highly relevant tissue but not readily available. This limitation imposes cross-sectional study designs and reduces sample sizes. Thus, when selecting tissues for epigenetic studies of human neurobehavior, it is important to consider the high tissue specificity of epigenetic marks, the relevance to neural development and the accessibility for prospective studies.

### Placental Epigenetics and Infant Neurobehavior

During intrauterine life, the placenta is the essential regulator of the fetal environment [28] and has been described as a third brain linking the mother and the infant [29]. Recent evidence suggests similarities between neuronal and placental DNA methylation profiles in areas associated with neuronal development genes [30]. In order to study epigenetic changes that occur during prenatal development and their relationship with infant neurobehavioral outcomes, we have explored placental epigenetic marks as functional biomarkers of the in utero environment in a large population-based cohort of healthy term infants: the Rhode Island Child Health Study (RICHS). We assessed newborn neurobehavior using the Neonatal Intensive Care Unit Network Neurobehavioral Scales (NNS), a comprehensive evaluation of neurobehavioral performance, including neurologic and behavioral measures and signs of stress [31]. Profiles of neurobehavior derived through NNS have previously shown to predict neurodevelopmental and cognitive performance in childhood [32].

Maternal cortisol influences the development of the fetal HPA axis and is metabolized through the placenta [33]. Thus, changes in the placental cortisol metabolism may alter infant neurobehavioral outcomes. We have analyzed epigenetic changes in the cortisol response genes *HSD11B2* and *NR3C1* within the RICHS cohort. *HSD11B2* inactivates cortisol by metabolizing it to cortisone, protecting the infant from excess glucocorticoids [34]. *HSD11B2* promoter methylation was associated with decreased quality of movement [35]. In an expanded study, we observed an interaction between maternal anxiety and *HSD11B2* methylation that contributed to infant hypotonia [36]. *NR3C1* encodes the glucocorticoid receptor, is expressed in the placenta and is involved in the metabolism of maternal cortisol. *NR3C1* placental methylation is positively associated with infant attention and quality of movement NNS scores and negatively associated with stress abstinence scores [37]. In a larger study,

**Table 1.** Human studies of epigenetics and neurobehavior

Gene(s), epigenetic change	Major findings	First author, year of publication
<i>Epigenetics and neurobehavioral disease</i>		
<i>MECP2</i> DNA methylation	<i>MECP2</i> promoter hypermethylation in the prefrontal cortex of male ASD cases. Lower brain <i>MECP2</i> expression in ASD cases.	Nagarajan et al. [19], 2006
<i>MECP2</i> DNA methylation	Increased methylation of a transition area (upstream of <i>MECP2</i> ) in the frontal cerebral cortex of male ASD cases. Aberrant <i>MECP2</i> promoter methylation in ASD female brain. <i>MECP2</i> methylation is locus-specific rather than global X chromosome changes.	Nagarajan et al. [20], 2008
<i>OXTR</i> DNA methylation	<i>OXTR</i> hypermethylation in the blood and temporal cortex of ASD cases. Decreased <i>OXTR</i> expression in the temporal cortex of ASD cases.	Gregory et al. [21], 2009
<i>RORA</i> , <i>BCL-2</i> DNA methylation	Differentially methylated genes in the blood of ASD cases enriched for transcription, nervous system development and cell death/survival. <i>RORA</i> and <i>BCL-2</i> exhibited decreased protein expression in tissue arrays (cerebellum and frontal cortex) in ASD cases. 8.1K CpG island array (HCGI8.1K).	Nguyen et al. [22], 2010
Genome-wide scan H3K4me3	Subset of ASD cases exhibited H3K4me3 spreading into nucleosomes in the prefrontal cortex. Identification of 711 loci with an altered H3K4me3 signal in the brain of ASD cases compared to that of controls. H3K4me3 peaks enriched in genes implicated in neurodevelopmental disease.	Shulha et al. [23], 2012
Histone methylation	Aberrant H3K4 methylation at a specific TSS is a predictor of transcriptional dysregulation.	
<i>EN-2</i> DNA and histone methylation	<i>EN-2</i> promoter hypermethylation in the cerebellar cortex associated with ASD, methylation is positively correlated with <i>EN-2</i> expression. Decreased histone H3K27 in the <i>EN-2</i> promoter in ASD cases.	James et al. [24], 2013
<i>PRRT1</i> <i>TSPAN32/C11orf21</i> Near <i>ZFP57</i> <i>SDHAP3</i> DNA methylation	3 DMRs in the temporal cortex: <i>PRRT1</i> (3'UTR) hypomethylation in ASD cases, <i>TSPAN32/C11orf21</i> hypomethylation in ASD cases, near <i>ZFP57</i> hypermethylated in ASD cases, 1 DMR cerebellum <i>SDHAP3</i> hypermethylated in ASD cases.	Ladd-Acosta et al. [25], 2013
<i>SHANK3</i> DNA methylation	<i>SHANK3</i> hypermethylation in the cerebellum and cerebral cortex of ASD cases compared to that of controls. Altered expression, an alternative splicing of <i>SHANK3</i> isoforms in brain tissue.	Zhu et al. [26], 2014
<i>DRD4</i> and <i>5-HTT</i> DNA methylation	Cord blood DNA methylation of <i>DRD4</i> and <i>5-HTT</i> regions are negatively associated with the ADHD symptom score at age 6.	van Mil et al. [27], 2014
<i>Placental epigenetics and newborn neurobehavior</i>		
<i>HSD11B2</i> DNA methylation	Inverse association between placental <i>HSD11B2</i> methylation and quality of movement scores in RICHs newborns. Pregnancy anxiety and placental <i>HS11B2</i> methylation (CpG4) interaction influence hypotonicity in RICHs infants.	Marsit et al. [35], 2012 Conradt et al. [36], 2013
<i>NR3C1</i> DNA methylation	Higher <i>NR3C1</i> placental promoter methylation is associated with higher quality of movement scores and lower infant attention scores in RICHs newborns. Potential interaction between methylation and genotype on infant attention score. Pregnancy depression and placental <i>NR3C1</i> methylation (CpG2) interaction influences self-regulation, hypotonicity and lethargy in RICHs infants.	Bromer et al. [37], 2013 Conradt et al. [36], 2013
<i>HTR2A</i> DNA methylation	Higher <i>HTR2A</i> placental methylation is associated with lower quality of movement and higher infant attention scores in RICHs newborns.	Paquette et al. [43], 2013
<i>LEP</i> DNA methylation	Higher <i>LEP</i> promoter placental methylation is associated with membership in a NNNS neurobehavioral profile marked by increased lethargy and hypotonicity and reduced risk of membership in a profile with opposite characteristics in RICHs newborns.	Lesueur et al. [47], 2014
Expression of 22 imprinted genes	Placental imprinted gene expression classes are associated with quality of movement and handling in RICHs newborns.	Marsit et al. [56], 2012
Expression of 6 placental miRNAs	Increased miR-16 placental expression is associated with reduced attention, increased miR-146a and miR-182 placental expression is associated with increased quality of movement in RICHs newborns.	Maccani et al. [51], 2013

*MECP2* = Methyl CpG-binding protein 2; *OXTR* = oxytocin receptor; *RORA* = RAR-related orphan receptor A; *BCL-2* = B-cell CLL/lymphoma 2; H3K4me3 = trimethylation of lysine 4 of histone 3; *EN-2* = engrailed homeobox 2; DMR = differentially methylated region; *PRRT1* = proline-rich transmembrane protein 1; *TSPAN32* = tetraspanin 32; C11orf21 = chromosome 11 open reading frame 21; *ZFP57* = zinc finger protein; *SDHAP3* = succinate dehydrogenase complex, subunit A, flavoprotein pseudogene 3; *SHANK3* = SH3 and multiple ankyrin repeat domains 3; *DRD4* = dopamine receptor D4; *SLC6A4* = solute carrier family 6; *HSD11B2* = hydroxysteroid (11-beta) dehydrogenase 2; *NR3C1* = glucocorticoid receptor; *HTR2A* = hydroxytryptamine (serotonin) receptor 2A; *LEP* = leptin; TSS = transcriptional start site.

we observed an interaction between maternal depression and *NR3C1* methylation on infant hypotonicity, lethargy and self-regulation [36]. Both *HSD11B2* and *NR3C1* promoter methylation are negatively associated with expression [35, 37], suggesting that infants with a higher methylation of these genes are exposed to increased cortisol. In humans, the cortisol response pathway influences infant cognitive development and physical maturation [38, 39]. Altered placental cortisol response may change infant neuromuscular and stress responses, as reflected in the infant's attention, stress-abstinence and quality of movement scores. Further analysis of other genes involved in cortisol response, such as *FKBP5*, is needed to fully understand the contribution of these epigenetic changes to infant neurobehavior.

Cortisol response and serotonergic tone are intimately linked, and serotonin can stimulate the HPA axis [34]. During fetal development, serotonin is important for the development of brain circuits [40], and the placenta acts as a transient source of serotonin during the early development [41]. Infants who experienced maternal depression in utero had decreased promoter methylation of the serotonin receptor *SLC6A4* in their blood [42], but we did not find associations between placental promoter methylation of *SLC6A4* and infant neurobehavioral outcomes within the RICHS cohort (unpublished data). Methylation of the serotonin receptor *HTR2A* was positively associated with NNNS attention scores and negatively associated with quality of movement [43]. This study provided evidence for epigenetics as a potential regulator of the placental serotonin response pathway, which influences behavioral outcomes. More research is needed to determine if other genes in this pathway are epigenetically regulated.

Rodent studies have linked the adipokine leptin (*LEP*) with neurodevelopment; leptin-deficient mice (*ob/ob*) display brain abnormalities and decreased locomotor activity [44]. Leptin is epigenetically regulated and produced by the placenta [45, 46]. Recently, we detected an association between higher *LEP* promoter methylation and increased odds of membership in a neurobehavioral profile characterized by lethargy and hypotonicity and with reduced odds of membership in a profile with opposite characteristics [47]. These observations were significant only in males and consistent with a marked negative correlation between methylation and *LEP* gene expression that was absent in placentas from females. These are the first results that link an energy-homeostasis gene with human neurobehavior and resemble the phenotype of *ob/ob* mice. Future research is needed to assess if epigenetic marks in other metabolic genes can influence neurobehavior.

MicroRNAs (miRNAs) post-transcriptionally target mRNAs and induce gene silencing, regulating a substantial amount of the mammalian genome [48]. miRNAs have been linked to placental functions and pathology and to neuronal survival and differentiation during development [49, 50]. We assessed placental expression of 6 miRNAs and their relationship to neurobehavior in the RICHS study [51]. Increases in miR-16 were associated with reduced attention scores, and increased miR-146a and miR-182 expression was associated with increased quality of movement scores. Some of the targets of these miRNAs are involved in the regulation of the serotonin [52], NF $\kappa$ B [53] and reward pathways [54]. This could help explain our observations regarding infant neurobehavior.

Imprinted gene expression is abundant in human placenta and is involved in growth and neural development [13, 55]. We observed associations between expression profiles of 22 placental-imprinted genes and quality of movement and handling scores of RICHS infants [56]. Quality of movement was associated with a decreased expression of the imprinted genes involved in neurological and motor functions during development, including *MEG3*, *HOXA11* and *HOXD10*. We also observed a high degree of correlation in the expression of adjacent imprinted genes, suggesting that in utero exposures produce coordinated expression changes and/or disrupt imprinting within control regions. Further research is required to determine the role of epigenetic marks in imprinted genes and infant neurobehavior.

## Future Directions

The field of neurobehavioral epigenetics is growing, with human studies complementing animal models. The human environment is multifaceted, and the fetus is exposed to nonspecific stressors, which are difficult to capture in laboratory conditions. The laboratory environment may induce epigenetic alterations independently of experimental conditions, confounding analysis. However, there are limitations to the observations made from human population studies. Epigenetic changes are tissue-specific [57]. The placenta is a relevant and accessible tissue for infant neurobehavioral studies [30], but we cannot definitely assess if these epigenetic patterns are conserved in brain tissue. These studies are also limited by their observational nature; we cannot establish mechanisms based on observed associations, and we cannot presently assess the prognostic value of neurobehavioral outcomes observed at birth. Most studies have used candidate gene approaches of targets known to be important in the developing brain, and we encourage validation of findings from candidate gene studies in different populations. However, this has a limited scope in complex neurobehavioral phenotypes, highlighting the need for epigenome-wide, agnostic analyses to identify novel genes that contribute to infant neurobehavior.

A number of neurobehavioral diseases exhibit sex differences in their prevalence and onset, including autism, ADHD and affective disorders [58]. Placental epigenetic marks also exhibit sexual dimorphism [47, 59–61], which could influence these neurobehavioral differences. More research is needed to define sexually dimorphic epigenetic patterning in autosomal loci and their potential role in infant neurobehavioral outcomes.

DNA sequence variation also exerts effects on epigenetic signatures across the genome [62]. Thus, it is important to consider possible contributions of single nucleotide polymorphisms to epigenetic regulation of neurobehavior. It has been suggested that individuals may be able to adapt to deleterious polymorphisms through epigenetic changes, which may explain the inability of these polymorphisms alone to predict disease [63]. In particular, monozygotic twins represent a desirable population to study because of reduced genetic confounding. Differential epigenetic patterning in combination with genetic factors may help explain differences in behavioral responses.

As our understanding of epigenetic changes and their role in newborn behavior increases, they could serve as biomarkers of neurobehavioral risk, facilitating early screening. In neurobehavioral diseases that manifest in early childhood, such as autism and ADHD, prompt interventions are important to improve long-term mental health [64, 65]. Future advancements may move this field beyond risk assessment to identification of prognostic biomarkers to evaluate response to therapy. The brain epigenome exhibits plasticity throughout life [66], and response to cognitive therapies alters gene expression [67, 68], which may be driven by epigenetic changes. Tracking responses to cognitive interventions through epigenetic markers could provide a quantitative assessment of therapeutic response. Pharmacologic agents that alter gene expression through epigenetic changes are established treatments for some psychiatric and neurologic conditions. This is the case for valproic acid, and it has been proposed that it could be used to correct epigenetic changes in cognitive disorders [69, 70]. Maternal cognitive intervention may induce epigenetic effects in offspring, as epigenetic changes have been observed in children born to mothers who underwent bariatric surgery [71]. More groundwork is needed to understand the normal epigenome, the consequences of its deregulation and the connection with mental health disorders before these tools can be used as functional biomarkers.

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