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When mummy and daddy get under your skin: A new look at how parenting affects children's DNA methylation, stress reactivity, and disruptive behavior

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Abstract

Child maltreatment is a global phenomenon that affects the lives of millions of children. Worldwide, as many as one in three to six children encounter physical, sexual, or emotional abuse from their caregivers. Children who experience abuse often show alterations in stress reactivity. Although this alteration may reflect a physiological survival response, it can nevertheless be harmful in the long run—increasing children's disruptive behavior and jeopardizing their development in multiple domains. But can we undo this process in at-risk children? Based on several lines of pioneering research, we hypothesize that we indeed can. Specifically, we hypothesize that highly dysfunctional parenting leads to an epigenetic pattern in children's glucocorticoid genes that contributes to stress dysregulation and disruptive behavior. However, we also hypothesize that it is possible to “flip the methylation switch” by improving parenting with known-effective parenting interventions in at-risk families. We predict that improved parenting will change methylation in genes in the glucocorticoid pathway, leading to improved stress reactivity and decreased disruptive behavior in children. Future research testing this theory may transform developmental and intervention science, demonstrating how parents can get under their children's skins—and how this mechanism can be reversed.

KEYWORDS

disruptive behavior, DNA methylation, parenting, stress reactivity

“One’s family [...] is like the chicken pox. You get this disease in childhood and it leaves scars for the rest of your life.”

(Jean-Paul Sartre) — for M.V.

Although meant figuratively, Sartre’s statement about the aftermath of early family experiences may be closer to the truth than once thought. We are beginning to learn how early family adversity can get under children’s skins and can leave biological marks—contributing to bio-regulatory processes that harm both children’s physical development and their mental health. In accordance, this paper reviews pioneering research on the biology of parenting. This research suggests that dysfunctional parenting leads to epigenetic profiles in children that, in turn, contribute to maladaptive stress response patterns and increased disruptive behavior. However, there is evidence that Sartre’s view on family life may have been overly pessimistic. Recent research suggests that the link between family adversity and psychopathology can be broken by what we coin “flipping the methylation switch.” By implementing effective parenting interventions that increase parental sensitivity, we may be able to produce epigenetic changes in the child’s glucocorticoid pathway genes, which in turn improve children’s stress reactivity and decrease their disruptive behavior, which is a common outcome of maladaptive parenting (e.g., McKee, Colletta, Rakow, Jones, & Forehand, 2008). But first, let us consider why it is so important to remediate children’s disruptive behavior.

1 | DISRUPTIVE BEHAVIOR: COSTS AND CONSEQUENCES

Disruptive behavior in childhood is characterized by disobedience, defiance of authority, angry or irritable mood, and verbal or physical aggression toward others (DSM-V; APA, 2013). Childhood-onset disruptive behavior marks a heightened risk for a subsequent diagnosis of conduct disorder and other psychopathologies in adulthood. Of all adulthood disorders, 25–60% can be traced back to juvenile disruptive behavior (Kim-Cohen et al., 2003). Many, if not most, children with disruptive behavior experience challenges in regulating their emotions and behaviors. Indeed, disruptive behavior in childhood can be considered an early marker of impulsivity and low self-regulation capacity (Bridgett, Burt, Edwards, & Deater-Deckard, 2015; Eisenberg et al., 2009), which both predict a heightened risk well into adulthood for the development of substance abuse, health problems, financial hardship, and delinquency (Moffitt et al., 2011; Von Stumm et al., 2011). The development of low self-control and disruptive behavior thus comes at great cost for the individual, but also for society at large. Specifically, costs associated with a high-risk youth dropping out of school, developing substance abuse, or engaging in a criminal career range from \$2.6 to \$5.3 million (Cohen, 1998; Cohen & Piquero, 2009). Also, children with conduct disorder diagnoses will cost society 10 times more, in terms of public service expenditure, than healthy peers by the time they reach age 28 (Scott, Knapp, Henderson, & Maughan, 2001). These costs relate to sick days at work, use of professional (mental) health care services, use of foster care and family support services, and crime-related costs. Thus, tackling childhood disruptive behavior early in life will yield tremendous gains, both for the individual and for society at large.

2 | PARENTING, CHILDREN’S STRESS REACTIVITY AND DISRUPTIVE BEHAVIOR

An effective prevention of disruptive behavior depends on our ability to identify its underlying etiology. One crucial etiological factor underlying the development of children’s

maladaptive stress reactivity and disruptive behavior lies in the early family context. Specifically, prolonged and severe dysfunctional parenting (such as with harsh and physical disciplining strategies used by parents and a lack of parental warmth and sensitivity) may lead to an altered pattern of stress reactivity in children. Such parenting encompasses, but is not limited to, established cases of maltreatment (Stoltenborgh, Bakermans-Kranenburg, Alink, & van IJzendoorn, 2015). It relates to both mothers' and fathers' highly dysfunctional parenting behaviors in the population at large. On the physiological level, effects of dysfunctional parenting may be reflected by functional changes in the autonomic nervous system (ANS) and the hypothalamic–pituitary–adrenal (HPA) axis (Boyce & Ellis, 2005). Although such alterations in stress reactivity may constitute an adaptive physiological response to a harsh or unpredictable parenting environment (Ellis, Bianchi, Giskevicius, & Frankenhuys, 2017), they may be harmful in the long run, leading to an increased “allostatic load” or physiological wear-and-tear on children's neuroendocrine, immune, metabolic, and cardiovascular and respiratory systems (McEwen, 2012; Solis et al., 2015).

In supportive parenting contexts, children's stress reactivity is characterized by a relatively quick stress response followed by a recovery and return to a resting state. However, with chronic and severe dysfunctional parenting—when the ANS and HPA axis are continuously activated—the stress response system may become less flexible in response to acute stress (Bunea, Szentágotai-Tátar, & Miu, 2017; Carpenter et al., 2007; Ha & Granger, 2016). This altered state can be measured in both the ANS and HPA axis; in the ANS by examining heart rate variability, and in the HPA axis by examining cortisol (a glucocorticoid stress hormone). A dysregulated stress reactivity pattern may show from blunted cardiovascular and cortisol responses to stress (Loman & Gunnar, 2010; Young-Southward, Svelnys, Gajwani, Enlow, & Minnis, 2020), and some previous research suggests that the cortisol response as well as (para)sympathetic reactivity to social stress is blunted in children and adolescents with maltreatment histories or who experienced dysfunctional parenting (McLaughlin et al., 2015; Oosterman, De Schipper, Fisher, Dozier, & Schuengel, 2010). However, contradicting evidence has emerged as well, with some studies instead showing hyperreactive stress patterns in at-risk children (Engel & Gunnar, 2020; Wesarg, Van den Akker, Oei, & Wiers, 2020). Although dysregulated stress reactivity patterns appear to be related to childhood disruptive behavior and conduct problems (Beauchaine, 2012; Bernard, Zwerling, & Dozier, 2015; Hinnant & El-Sheikh, 2013), an unanswered question remains: to what extent do (epi)genetic factors account for the relationship between dysfunctional parenting on the one hand, and children's stress reactivity and disruptive behavior on the other hand?

3 | (EPI)GENETICS IN PARENTING EFFECTS ON DISRUPTIVE BEHAVIOR

Stress reactivity is known to have a genetic basis (Eisenberg, Spinrad, & Eggum, 2010) and for disruptive behavior specifically, meta-analyses of behavioral genetic studies have demonstrated that children's genotype accounts for roughly one third of the variance in aggression, crime, and DSM-IV conduct disorder symptoms (Rhee & Waldman, 2002, 2007). In the candidate gene era, several meta-analyses indicated that based on specific genetic mutations, for example, the Monoamine Oxidase-A (MAOA) gene and several genes in the dopaminergic pathway (Dopamine Receptor D2 (DRD2) and DRD4 genes) children responded differently to maltreatment and (dys)functional parenting (Bakermans-Kranenburg & Van IJzendoorn, 2011; Byrd & Manuck, 2013). Interestingly, across a series of randomized controlled trials (RCTs)—yielding superior power and methodological rigor in testing gene–environment interplay (see Dodge, 2009; Moffitt, 2005)—these gene–environment interactions were found to follow a differential susceptibility, or

“for better and for worse” pattern—that is, children with specific genotypes suffered more from adverse environments, but also benefited more from enriched environments (Van IJzendoorn & Bakermans-Kranenburg, 2015). For example, a recently conducted RCT of the Incredible Years parenting program showed that the intervention increased positive parenting and reduced child disruptive behavior (Weeland et al., 2017), but also showed that these effects were stronger in boys with a higher score on a polygenic index that comprised genes involved in a dopaminergic pathway (DAT1, DRD2, DRD4, MAOA, and COMT). This revealed that, based on their genotype, children may not only be more susceptible to negative parenting, but may also reap more benefit from (intervention-induced) improvements in parenting (Chhangur et al., 2017).

Despite these initial promising findings, a recent systematic review demonstrated that gene–environment interaction research on disruptive behavior has yielded many contradictory and unreplicated findings (Weeland, Overbeek, de Castro, & Matthys, 2015), which currently allows no definite conclusions about children’s gene-based response to parenting. Thus, while we know that genetic variance contributes to the development of disruptive behavior, we have so far been unable to fully characterize genetic variance in terms of specific, measured alleles. This “missing heritability problem” (Plomin, 2013) may have arisen because the candidate gene model is misspecified and overly simplistic. It seems more logical to assume that gene–environment interplay is polygenic in nature, that it is functionally explained by a neurobiological intermediate phenotype, and that it co-dependes on the dynamic expression of genetic material, rather than only on children’s genetic code (Dick et al., 2015). The missing heritability problem thus emphasizes a clear need to move toward a different approach: examining (a) biologically plausible, polygenic pathways and (b) regulators of genetic expression, such as epigenetics, that contribute to complex phenotypes such as children’s stress-reactivity and disruptive behavior.

3.1 | Polygenic approaches

Establishing a sound polygenic measure for the glucocorticoid pathway is crucial, because this allows for a reliable and precise identification of the gene-stress reactivity–disruptive behavior pathway. In order to do justice to the true level of genetic complexity polygenic constructs ideally contain multiple, weighted genetic variants. In recent research on disruptive behavior, this has been done in a data-driven approach—building polygenic scores based on outcomes of previous genome wide association studies (GWAS) on antisocial behavior and aggression (Pappa et al., 2016; Tielbeek et al., 2017) but also on educational attainment (Okbay et al., 2016)—a construct that may be related to self-regulation and individuals’ ability to inhibit disruptive behavior impulses. For example, in a pioneer study on the well-known E-Risk and Dunedin data, Wertz et al. (2018) created a polygenic score by averaging weighted counts across all single nucleotide polymorphisms (SNPs) that could be matched with SNPs reported in the results of the most recent, largest-ever GWAS on educational attainment ($n = 293,723$; Okbay et al., 2016). Using this approach, Wertz et al. (2018) found that a lower polygenic education score predicted criminal offending—over and above the effects of a criminogenic family environment. Interestingly, the polygenic score was also found to predict lower cognitive abilities and self-control, which mediated the association between the polygenic education score and criminal offending.

Other approaches in constructing polygenic scores related to disruptive behavior have capitalized on a pre-specified neurobiological pathway, in which putative genetic variants should be interconnected. For example, Elam, Clifford, Shaw, Wilson, and Lemery-Chalfant (2019) applied gene set enrichment analysis to meta-GWAS data to create developmentally

targeted, functionally informed Polygenic Risk Scores (PRS). Using two developmentally matched meta-GWAS discovery samples, separate PRS for aggression were formed, then examined in time-varying effect models of aggression in a second sample of children, followed longitudinally across early and middle childhood. The functional PRSs were then found to be associated with elevated and increasing aggression in both the early and middle childhood models.

3.2 | Epigenetic approaches

The term epigenetics refers to biochemical modifications of the DNA that influence gene expression without altering the DNA sequence itself. DNA methylation is the most widely studied epigenetic process in humans. In this process, a methyl molecule (CH_3) is covalently bonded to a cytosine molecule at a cytosine–phosphate–guanine (CpG) site. Gene expression can be altered when DNA methylation occurs at the actual site of the gene or within its promoter region (Meaney, 2010; Szyf & Bick, 2013). DNA methylation prevents transcription of the DNA, typically leading to downregulation or silencing of gene expression. Methylation is an epigenetic process through which early family experiences may be biologically embedded. In this paper, we hypothesize that dysfunctional parenting may lead to methylation of genes that code for the functioning of children's glucocorticoid–stress reactivity–system, leading to diminished stress regulation. The first line of evidence to support this hypothesis comes from animal models. Several pioneering rodent studies (e.g., Francis, Diorio, Plotsky, & Meaney, 2002; Weaver et al., 2004) showed that adverse caregiving conditions—maternal separation and low pup licking/grooming and arched-back nursing by rat dams—altered offspring methylation in a glucocorticoid receptor (GR) gene, as well as GR gene expression and HPA-axis stress response. This suggests a causal link between parenting, glucocorticoid gene expression, and stress reactivity.

Preliminary findings now suggest similar mechanisms may operate in humans. Several studies have found an association between methylation levels at a number of genes and exposure to early life adversity, such as maltreatment and parental separation (Jiang, Postovit, Cattaneo, Binder, & Aitchison, 2019; Vinkers et al., 2015). In particular, hypermethylation at the glucocorticoid receptor (GR) gene, a key regulator of the HPA axis, has been repeatedly found in individuals who have experienced early life adversity (for a review see Palma-Gudiel, Córdova-Palomera, Leza, & Fañanás, 2015). In two of these studies greater GR gene methylation and reduced GR gene expression was found in cells of the hippocampus—a brain region involved in stress regulation—in suicide victims exposed to childhood maltreatment (Labonte et al., 2012, McGowan et al., 2009). Moreover, an association has also been found between GR gene hypermethylation and both emotion regulation difficulties and externalizing behavior in children (Cicchetti & Handley, 2017). Most research has focused on the role of the primary caregiver, typically the mother; only very few studies included fathers. Nevertheless, one study found an association between paternal mental health problems and child DAT1 methylation (Cimino et al., 2018). Together, these findings suggest a plausible link between GR gene hypermethylation, diminished stress reactivity, and child disruptive behavior in those exposed to dysfunctional parenting.

Although promising, the available body of evidence should be treated with caution as most studies until now have relied on relatively small sample sizes, often used a single candidate gene approach, and have been cross-sectional—often retrospective—in research design. A recent review by Provenzi, Brambilla, di Minico, Montirosso, and Borgatti (2019) is illustrative of this trend, showing that out of 11 studies of methylation and maternal behavior only 4 ($n \leq 128$) had a prospective design. Moreover, although childhood

adversity has been linked to differential DNA methylation, previous research has not established whether DNA methylation mediates a link between dysfunctional parenting and subsequent stress reactivity and disruptive behavior. Instead, most previous research has focused either on the link between adverse parenting and DNA methylation or on the link between DNA methylation and child developmental outcomes (Mulder, Rijlaarsdam, & Van IJzendoorn, 2017). A crucial next step, therefore, is to use a prospective design following children from infancy onward, to examine whether there is a full causal chain from dysfunctional parenting to disruptive behavior, via DNA methylation and altered stress reactivity. Studying children from early infancy onward is particularly important. Recent analyses based on the Avon longitudinal study of parents and children (ALSPAC) demonstrated that effects of early adversity on DNA methylation at 7 years of age strongly depended on timing of exposure—with exposure before 3 years of age explaining almost all variance in epigenetic outcomes (Dunn et al., 2019). This result fits with an evolutionary-developmental theory of “biological sensitivity to context” (Boyce & Ellis, 2005), which holds that there is a sensitive period during the perinatal phase and early infancy for the development of stress reactivity. Together with the Dunn et al. (2019) findings, this may suggest that the epigenome is more malleable to adverse environmental factors, such as dysfunctional parenting, in early infancy.

4 | FLIPPING THE METHYLATION SWITCH

In addition to limited knowledge of the psychobiological pathways that underlie the link between dysfunctional parenting and children’s disruptive behavior, little is known about whether this chain can be broken. Can the differential methylation of genes responsible for children’s stress-reactivity and disruptive behavior actually be reversed following an earlier exposure to dysfunctional parenting? And will this lead to a longer-term reduction in disruptive behavior? To gain more insight into this matter, it is essential to set up randomized experiments or case–control studies in which dysfunctional parenting is manipulated. Is this possible in humans? It is commonly contended that it would be unethical to manipulate early adversity. However, this contention is based on a one-sided view that focuses on inducing risk rather than inducing resilience. Of course, it would be unacceptable to induce risk in families, but it is ethical—if not desirable—to promote resilience within at-risk families. A randomized experiment or case–control study can causally investigate early adversity as long as (a) it takes place within a population of families that are at-risk and (b) an experimental group takes part in a known-effective intervention aimed at improving family functioning and child disruptive behavior, which can be compared to a (wait-list) control group of at-risk families.

Why is working with experimental designs indispensable if we want to learn more about (epi)gene–environment interplay? First, by randomizing children across experimental conditions in which the parenting environment is manipulated, experimental studies can rule out alternative explanations. In correlational studies, parenting “effects” on DNA methylation may be confounded by children’s other life events or pathologies (Dick et al., 2015; Overbeek, 2017). Second, experimental studies have superior statistical power compared to correlational designs (McClelland & Judd, 1993)—a major issue in (epi)genome wide association studies and studies on (epi)gene–environment interplay alike. More specifically, experimental designs yield more than a fivefold increase in statistical power to detect interactions (Howe, Beach, & Brody, 2010). But perhaps the most important advantage of using an experiment is that it may help us examine whether we can “flip the DNA methylation switch.” Indeed, we hypothesize that by using a known-effective

intervention to promote parental warmth, sensitivity, and more appropriate disciplining techniques, a hypermethylated glucocorticoid gene pathway will demethylate. This may lead to normalized stress responses, improved self-regulation and less disruptive behavior.

Although at first glance our hypothesis may seem far-fetched, the results from several intervention trials suggest that a “behavioral programming effect,” as described above, may be within reach. Specifically, RCTs of various family support and parenting interventions have demonstrated improvements in children’s biological stress reactivity. For example, a meta-analysis showed that family and parent interventions stimulated the normalization of cortisol reactivity among groups of at-risk children aged 0–18 years (Slopen, McLaughlin, & Shonkoff, 2013). Specific evidence comes from several different individual RCTs on at-risk groups and subgroups of maltreated and foster children (Bell, Shader, Webster-Stratton, Reid, & Beauchaine, 2018; Cicchetti, Rogosch, Toth, & Sturge-Apple, 2011; Dozier, Peloso, Lewis, Laurenceau, & Levine, 2008; Fisher, Van Ryzin, & Gunnar, 2011). Another RCT of a family-oriented psychosocial intervention among African-American youths, found intervention-induced reductions in blood inflammation levels in adolescents, a proxy for improved stress regulation (Miller, Brody, Yu, & Chen, 2014). These findings are promising because they indicate that parenting interventions can have a positive, “normalizing” effect on physiological reactivity, suggesting it is possible to repair children’s bio-regulatory systems following early childhood adversity.

In rodent studies, the reversibility of adverse caregiving effects on DNA methylation has already been demonstrated. For example, well-known studies by Francis et al. (2002) and Weaver et al. (2004) have shown that it is possible to chemically demethylate the glucocorticoid receptor gene, reversing the effects of maternal separation and low pup licking/grooming and arched-back nursing by rat dams. Some first findings on humans have recently also been published, related to the potential reversibility of the effects of early adversity on DNA methylation (O’Donnell et al., 2018). This study concerned data from the Nurse Family Partnership (NFP), an intervention program that targets mothers at risk for abusive parenting. The 188 participants in this study were born to women randomly assigned to control ($n = 99$) or nurse-visited intervention groups ($n = 89$) and provided blood samples and a diagnostic interview at age 27 years. Analyses showed that the NFP program and a history of abuse were both significantly associated with DNA methylome variation at 27 years of age, independent of gender, ancestry, cellular heterogeneity, and a polygenic risk index for major psychiatric disorders. Another study (Hoye et al., 2019) focused on epigenetic effects of the Attachment and Biobehavioral Catch-up (ABC) intervention, a 10-session manualized intervention that is designed to enhance parenting behaviors that stimulate effective self-regulation in children aged 6–21 months, who were referred to local child welfare agencies due to concerns of maltreatment. While there were no group differences in DNA methylation patterns pre-intervention, DNA methylation significantly varied post-intervention between ABC and control children at 14,828 CpG sites, which involved gene pathways related to cell signaling, metabolism, and neuronal development. Although only preliminary in nature, due to its rather small sample size, the study provides proof of principle, in that parenting interventions can lead to epigenome wide changes in children’s DNA methylation over time.

On a practical level, successfully studying the effects of parenting interventions on children’s DNA methylation, stress reactivity, and disruptive behavior only makes sense if there is sufficient evidence to suggest that these parenting interventions are effective. Indeed, there is strong evidence from a previous meta-analysis (Menting, de Castro, & Matthys, 2013) that the effect size for parenting interventions in at-risk populations of families is sizable (Cohen’s $d = .60$), a result recently corroborated in an individual participant data meta-analysis of Incredible Years trials (Leijten et al., 2018). Furthermore, recent analyses

have shown that parenting interventions are even more effective for families that are most at-risk and can lead to clinically relevant reductions in child disruptive behavior (Van Aar et al., 2019; Weeland et al., 2017; Weeland, van Aar, & Overbeek, 2018). For example, in our trial of the Incredible Years parenting program, we found that of all children in the clinical range for disruptive behavior at pre-test, 60.3% were no longer in the clinical range at post-test and 65.1% were no longer in the clinical range at follow-up (unpublished findings). Notably, parenting intervention effects are sustained in the longer term (Van Aar, Leijten, de Castro, & Overbeek, 2017), not only on disruptive behavior but also on internalizing problems, self-esteem, and academic outcomes (Sandler, Schoenfelder, Wolchick, & MacKinnon, 2011). These long-lasting effects of parenting interventions in at-risk families, makes them a suitable tool for manipulating early adversity, that can help us unravel the psychobiological effects of dysfunctional parenting on disruptive behavior.

5 | FUTURE OUTLOOK: RESEARCH AGENDA AND MAIN RESEARCH OBJECTIVES

The hypotheses outlined in this paper are currently being examined in the Joint (Epi)genetics Of Parenting And stress-Reactivity in the Development of Youths (JEOPARDY) study: a new, large-scale, longitudinal-experimental study among 12–14 month old at-risk children and their parents, who are participating in the Amsterdam SARPHATI cohort (named after Samuel Sarphati, a renowned 19th century general practitioner and benefactor who was responsible for many improvements in Dutch public health practice, and who started up many initiatives to eradicate poverty). The SARPHATI cohort has an expected influx of roughly 10,000 Amsterdam-based newborns and families each year, which will be followed with regular consultations by the Amsterdam “parent-child teams,” who keep track of children’s health and development up to 18 years of age. During a consultation in the infancy period, one parent per child is screened for parenting stress using a standardized and well-validated questionnaire. All parents who score above the 75th percentile on this screening are eligible for inclusion. JEOPARDY has a multi-informant, multi-method approach and pairs (epi)genetic and physiological stress-reactivity data with data from online questionnaire assessments, observations of parent-child interactions, and child behavior regulation tasks during home visits to the participating families.

JEOPARDY has two research lines: a 3-year, 6-wave prospective cohort study (*research line 1*) and a stepped-care effectiveness study, consisting of two back-to-back RCTs of the Video-feedback Intervention to promote Positive Parenting and Sensitive Discipline (VIPP-SD) and the Family Check-Up (FCU) intervention, respectively (*research line 2*). All research hypotheses are specified in Table 1, which are integrated into the study’s conceptual model, depicted in Figure 1. The study will also be enriched by child DNA methylation data from a prior RCT on the Incredible Years parenting program (Chhangur & Weeland et al., 2012). These data will be used to build polygenic scores to assess the contribution of children’s genotype in our theoretical models.

If successful, the proposed research agenda may contribute to transforming our developmental and intervention science by showing how parenting affects children’s biology and can lead to child disruptive behavior and later life psychopathology through the process of DNA methylation. Yet, there are several questions and caveats that should be considered in relation to this research agenda. To name a few, first, it is important to keep in mind that DNA methylation is a proxy for, rather than a direct measure of gene expression. Thus, we assume that methylation levels are in some way indicative of the extent to which nearby genes are expressed through mRNA activity—an assumption that appears

TABLE 1 Hypotheses informing longitudinal and experimental research lines

| Research line 1: Prospective-longitudinal study | Research line 2: Stepped-care study with randomized trials |
|--|--|
| Hyp. 1.1 Dysfunctional parenting leads to differential DNA methylation of glucocorticoid genetic pathway in children. | Hyp. 2.1 Effective parenting interventions lead to improved (more positive and sensitive) parenting behavior. |
| Hyp. 1.2 DNA methylation of glucocorticoid genetic pathway leads to dysregulation of stress reactivity in ANS and HPA axis. | Hyp. 2.2 Improved parenting leads to a DNA demethylation of glucocorticoid genetic pathway in children. |
| Hyp. 1.3 Dysregulation of stress reactions in the ANS and HPA axis leads to increases in children's disruptive behavior. | Hyp. 2.3 DNA demethylation of glucocorticoid genetic pathway leads to normalization of stress reactivity and disruptive behavior. |
| Hyp. 1.4 Children's disruptive behavior reinforces dysfunctional parenting which further increases the risk of developing a dysregulation of stress reactivity. | Hyp. 2.4 Parenting intervention effects on children's bio-regulatory system (DNA demethylation, stress reactivity) are dose dependent—become stronger with more prolonged intervention efforts. |

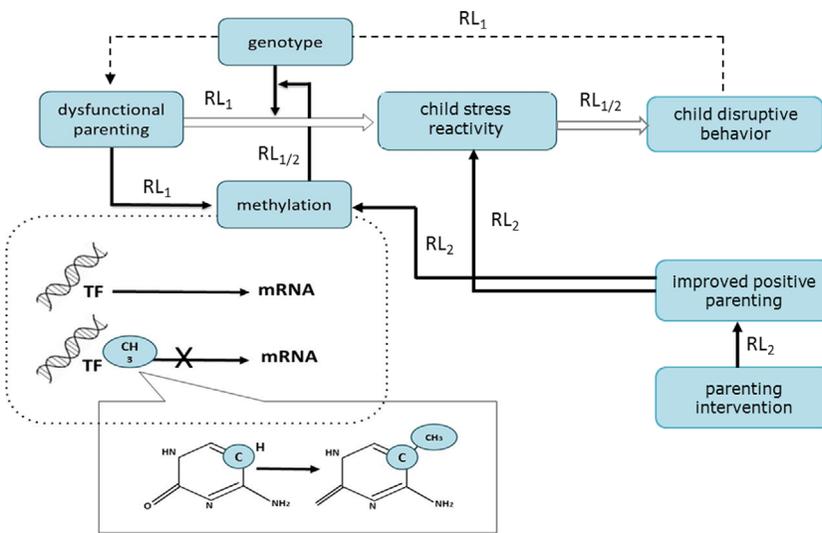


FIGURE 1 Conceptual overview of relations between dysfunctional parenting and children's (epi)genotype, stress reactivity, and disruptive behavior
 Note. RL₁/RL₂, research line 1/research line 2; mRNA, messenger RNA (ribonucleic acid); TF, transcription factor

viable (see Palma-Gudiel et al., 2015)—but we cannot be sure of the causal effects of DNA methylation on gene expression without also measuring RNA quantities. Another question relates to which tissue type provides DNA methylation estimates that have the strongest relationship with children's brain function. Research suggests that saliva samples show the larger correlation with brain functioning than blood samples (Smith et al., 2015) and suggests that the methylation estimates from saliva samples significantly correlate with brain tissue methylation measured across the epigenome (Braun et al., 2019). Third, it is important to examine possible sex differences in elucidating the full causal chain from early environmental adversity to methylation and stress reactivity, as well as

to examine methylation effects not only on disruptive behavior, but also on related phenotype expressions related to temperament, such as negative reactivity and “difficult” temperament.

Research until now has (a) not elucidated the full causal chain from parenting to disruptive behavior via DNA methylation to children’s stress reactivity, and (b) has not attempted to trigger DNA methylation changes within the glucocorticoid gene pathway by using a large-scale, stepped-care parenting intervention design. Another innovative aspect of this research concerns the experimental (RCT) design—focused on flipping the DNA methylation switch by implementing more positive, enriched parenting in at-risk families. Instead of investigating child DNA methylation at only an associational level, it is essential to attempt to manipulate the DNA methylation process itself. Using this method opens up the possibility of establishing that children’s epigenomes can be “behaviorally reprogrammed” and that parenting interventions can provide long-lasting effects, in part through their ability to reset children’s biological stress system.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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