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DOI:

[10.1159/000486683](https://doi.org/10.1159/000486683)

Document Version

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Citation for published version (APA):

Barker, E. (2018). Epigenetics, early adversity and child and adolescent mental health. *Psychopathology*.
<https://doi.org/10.1159/000486683>

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Running Head: EPIGENETICS AND MENTAL HEALTH

IN PRESS; PSYCHOPATHOLOGY

Epigenetics, early adversity and child and adolescent mental health

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Conflict of interest: No conflict of interest is declared.

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Acknowledgements

This manuscript was supported by the National Institute of Child and Human Development grant (R01HD068437). I thank Esther Walton and Alan J. Meehan for comments on a previous version of this manuscript.

Abstract

Epigenetic modifications, such as DNA methylation (DNAm), can help explain how early adversities can engender long-term vulnerability for mental health problems. At present, there is preliminary evidence to support the possibility of epigenetic mediation: environmental factors are reported to influence offspring DNAm, which in turn, associate with child and adolescent psychopathology. However, all analyses have been correlational in nature and, as these studies have focused on children and adolescents, DNAm has been based on peripheral tissue (cord blood, whole blood, buccal cells). Therefore, the extent to which DNAm could represent a causal mechanism (e.g. a surrogate of central nervous system function) or a biomarker (i.e. an indicator of the pathological process leading to disease) is unclear. This short report has two main components. First, two studies are summarised, one a candidate gene study and the other an epigenome-wide association study, in which DNAm was reported to (partially) mediate the link between adversity and child development. Second, there is a discussion of (i) the “tissue issue”, (ii) maximizing the interpretability of candidate gene and epigenome-wide approaches, and (iii) the need for examining DNAm as a potential biomarker for mental health. It is argued that advances within these three areas will make clearer the role of DNA methylation in the link between adversity and child and adolescent mental health.

Keywords: DNA methylation; Epigenetics; Developmental Psychopathology; Childhood; Adolescence; Adversity; Mediator; Biomarker

Introduction

DNA methylation (DNAm) – an epigenetic process that can regulate gene expression – has emerged as a potential mechanism through which the genome can capture the effects of early adversity and propagate their influence [1]. The ideas of ‘capturing’ and ‘propagating’ summarize a mediational hypothesis: that early adversity can have long-term mental health effects (at least partially) via changes in DNAm. However, at present, very few existing studies have adopted longitudinal designs capable of testing mediation (i.e. adversity → DNAm → mental health) – hence, published ‘mediational’ studies are rare [see 2]. Moreover, as these studies have focused on living children and adolescents, they have examined DNAm from peripheral tissues (e.g. cord blood, whole blood, saliva), but arguably brain tissue is more relevant for mental health. As a result, it is not clear if DNAm is a causal mechanism in the aetiology of mental health problems (Figure 1a), **or a biomarker, in this case, a quantitative index of environmental adversity that may be independent of disease aetiology** (Figure 1b). Herein, two recent DNAm mediation studies are reviewed, followed by a discussion of three key areas that could help clarify the role of DNA methylation in the link between adversity and mental health.

Epigenetics and DNA Methylation

Prior to reviewing the mediation research, epigenetics and DNAm will be (briefly) defined. Epigenetic mechanisms influence dynamic changes in gene transcription independent of the genomic DNA sequence, primarily via modifications to DNA, histone proteins, and chromatin structure [3]. One of the most extensively researched epigenetic mechanisms is DNAm, which refers to the addition of a methyl group, primarily in the context of cytosine-guanine (CpG) dinucleotides [3]. In the human genome, CpG sites often cluster in CpG-islands, which themselves tend to be embedded in promoter regions of genes. Methylated CpG islands impede transcription factors from accessing the DNA sequence. Increased methylation in these regions is typically associated with inhibition of gene transcription (i.e. gene silencing) and chromatin compaction. Importantly, because epigenetic processes have been shown to respond to both genetic [4] and environmental [5] influence, they represent a potential mechanism that can help explain the biology of gene-environmental interplay and disease susceptibility across the lifespan [6].

DNA methylation mediation studies

The ‘promise’ of a mediational framework is that – if adversity-related DNAm is a causal link in the aetiology of a mental health problem – then reversing epigenetic marks might help in remission of these problems. Although causality has yet to be established and

reduced power is an ongoing concern, research has nevertheless demonstrated that DNAm may act as a ‘mediator’ in the link between adversity and child outcomes, and hence offer a potential target for intervention [see 5]. There is good evidence in animal and human studies that prenatal stress can have long-term effects on the child, such as affecting neurodevelopment. Here, vulnerability for psychiatric disorders could – in part – be due to increased exposure to cortisol and its impact on foetal brain development [7, 8]. In the first study of its kind, Monk et al. [9] examined placental DNA methylation as a potential pathway in the link between pregnant women’s (n = 61) distress and offspring aberrant development (in utero). They reported higher perceived maternal stress in the second trimester (24-27 gestational weeks) associated with higher methylation of *HSD11B2*, which is an important placental barrier gene that inactivates cortisol (a correlate of psychological stress). Higher DNA methylation of *HSD11B2*, in turn, associated with a lower score on an index of foetal neurodevelopment, the assessment of which took place in the third trimester (34-37 weeks). The authors stated that increased DNA methylation of *HSD11B2* could lead to the downregulation of the placental barrier enzyme, hence a pathway to elevated in utero exposure to stress-related cortisol.

In another mediation study, a ‘hypothesis free’ genome-wide strategy was taken. This approach allows for the discovery of novel biological correlates (as opposed to testing a priori defined candidate genes), which can aid in the development of more holistic etiologic knowledge. Here, Cecil et al. [10], using the epidemiological birth cohort, the Avon Longitudinal Study of parents and Children, examined a subset of youth (n = 244) who were oversampled for early onset conduct problems (i.e. before age 10; lying, fighting, stealing). The researchers tested epigenome-wide, prospective associations between DNA methylation (birth, age 7) and substance use in adolescence (tobacco, alcohol and cannabis use; age 14–18). It was reported that at birth (but not at age 7), epigenetic variation across a tightly interconnected genetic network (n = 65 epigenome-wide significant loci) associated with higher levels of substance use. Key annotated genes included *PACSIN1*, *NEUROD4* and *NTRK2*, implicated in neurodevelopmental processes. In addition, prenatal maternal tobacco smoking prospectively associated with adolescent substance use via the epigenetic variation of these 65 loci (i.e. a poly-epigenetic risk score). Of interest, several of the 65 loci were associated with known methylation quantitative trait loci [see 4], which means that the levels of DNA methylation are likely under a degree of genetic influence. In fact, the loci that associated with methylation quantitative trait loci (‘under genetic influence’) showed higher

continuity between birth and age 7 than the loci that were not associated with methylation quantitative trait loci ('not under genetic influence').

Discussion

Although the above studies show that DNAm can act as a mediator between risk exposure and child psychopathology, it is important to note that they are correlational in nature (non-causal). Below, three key areas are discussed that can help clarify the role of DNAm in the link between adversity and mental health. We note that other areas not covered here are also important, such as genetic influence, cellular heterogeneity, temporal variability, replication and functional characterisation of DNAm [see 2, 11].

1. The issue of peripheral tissue as a surrogate for central nervous system (CNS) function

Although the brain may be of ultimate interest, for studies on living persons, available options include collecting accessible peripheral tissues such as saliva, buccal epithelial cells or blood. A major debate has centred on the utility of peripheral tissues for mental illnesses that primarily manifest in the brain [12]. Indeed, studies on the correlation between peripheral and CNS show mixed patterns: while a majority of CpGs do not show intra-individual associated, a minority do [13] – especially those under genetic influence [14, 15].

A strategy worth considering is to target mental health problems that have mechanistic underpinnings in other tissues, including blood [12]. Blood is a primary tissue for research focused on immune response and peripheral inflammation [16, 17]. Indeed, a wide-range of psychiatric disorders have been associated with peripheral inflammation and altered immune response [18]. Moreover, there is good evidence from animal studies, and increasing evidence in humans, that peripheral inflammatory markers can affect brain areas implicated in certain psychiatric disorders [19, 20]. Consequently, adversity-related immune processes and DNAm may be well measured in blood samples.

2. Candidate gene vs genome-wide strategies

Early DNAm studies, before the advent of genome-wide techniques, focused on specific candidate genes that were selected *a priori*, due to known functional relevance for certain mental illnesses. This strategy is best with highly targeted research questions (as in Monk [11] investigating placental barrier genes). However, given the discussion directly above, a complimentary approach is to not only focus on candidate genes involved in inflammatory response, but also on whole systems that functionally interrelate with immune response and brain development, such as the hypothalamic pituitary adrenal axis [20]. The suggestion here is to prioritize candidate genes or systems that have plausible pathways to the

CNS. Of note, several online databases catalogue known associations of DNAm between peripheral and post-mortem brain samples [14, 15].

In recent years, genome-wide DNAm studies have become more popular, due to their increased affordability and data content [11]. The Cecil et al. study reviewed above may be an exemplar, as the top loci formed a network that was plausibly linked with neurodevelopmental risk for substance use. However, not all genome-wide studies have clear-cut results. Given that intra-individual variation in a majority of the peripheral-based CpGs in genome-wide arrays tend not to co-vary with those in the brain [14, 15], one may question is if it is worth examining these arrays in their entirety. For researchers interested in maximizing CpGs likely to associate with brain-based mental illnesses, an *a priori* set of CpGs (e.g. a ‘systems approach’) could be isolated from the array data, which could still span thousands of loci [see 21]. Again, the suggestion is to prioritize CpGs within biological systems that are believed to associate with CNS function. An alternative approach could be to prioritize CpGs with underlying methylation quantitative trait loci (mQTLs), which have been validated in both peripheral and CNS tissues [14].

3. Establishing DNAm as a biomarker

Blood-based DNAm studies have shown promising associations with respect to both environmental adversity and mental illness [12]. One promising avenue is to establish DNAm as a biomarker for mental illness. For biomarkers to be useful, they must be cost effective, drawn from accessible tissue and predictive of future risk [22]. One advantage of a biomarker is that it does not have to be mechanistic (i.e. CNS surrogate) [Figure 1, panel b; see also 22]. Indeed, blood-based biomarkers have been used for diagnostics, predictive risk, disease monitoring and/or treatment response in cancer, cardiovascular and infectious disease [23, 24]. Although biomarkers for brain-based disorders (Alzheimer’s disease, depression) have proven more difficult to establish [24], using a genome-wide approach based on blood tissues across 13 population-based cohorts, Liu, Marioni [25] reported that a set of 144 CpGs discriminated drinkers from non-drinkers (area under the curve: >0.90). It was suggested that a blood-based DNAm diagnostic test could be developed to validate self-report data, in a forensic setting or as a screening test. However, as the Liu, Marioni [25] study was cross-sectional, the authors noted that they could not rule out reverse causality (i.e. DNAm may be caused by alcohol intake); therefore, additional research is needed to determine if the set of 144 CpGs could be predictive of problematic levels of future alcohol usage.

The recent interest in epigenetics, from a developmental psychopathology perspective, stems from the potential of DNA methylation – whether as a causal mechanism

or as a biomarker – to index both exposure to adversity and vulnerability for mental health problems [2]. Toward this end, there has been substantial activity the ‘epigenetics’ of adversity-related disorders, such as post-traumatic stress disorder [26] and borderline personality disorder [27]. Of interest, DNA methylation in genes that underlie stress response, neurotransmitter activity and immune regulation have been identified [27]. These preliminary findings may provide a useful framework for more in-depth investigations of both the pathogenesis and clinical responsiveness of these disorders. For example, if adversity affects peripheral DNA methylation in a gene, which, in turn, reliably increases vulnerability for borderline personality disorder (i.e. high predictive specificity), then an efficacious intervention may also show change in both DNA methylation of the candidate gene and mental health symptoms for responders versus non-responders (i.e. a potential causal mechanism in symptoms). Although this area of research is in early stages, certain small scale (proof of concept) interventions have reported joint change in DNA methylation of candidate genes and symptoms of mental health problems including borderline personality [28] and anxiety [29]. Large scale randomised controlled trials are needed to increase scientific rigor and to establish causality. Application of epigenome-wide methods [e.g. see 30, 31] may be especially useful for the discovery of novel biological systems that may be mechanisms – or biomarkers – of treatment response and symptom change.

Figure 1. The potential of DNA methylation (DNAm) within developmental psychopathology studies. A. DNAm as a causal biological mechanism, associating with environmental adversity and subsequent vulnerability for mental health problems. B. DNAm as an adversity-related biomarker of subsequent mental health problems. Note. Other epigenetic markers, such as histone modification, can be used in the same way as DNAm.

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