Commentary

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Early-Life Adversities and Epigenetic Modifications: The Impact on Brain Development, Synaptic Function, and Stress Response

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In a recent article published in *Biological Psychiatry: Global Open Science*, Francis *et al.* (1) mainly aimed at comprehensively mapping genome-wide DNA methylation in the prefrontal cortex (PFC) of rats following maternal separation (MS). The authors found a total of 33,905 differentially methylated cytosines (DMCs) and 151 differentially methylated regions (DMRs) among rats in the MS group. Importantly, according to the functional analysis of the dysregulated genes by DMCs and DMRs in the promoter or gene body, a gene enrichment that is critically involved in synaptic plasticity, stress response, and brain development was reported. Relevantly, the authors stressed the implications related to specific methylated genes such as *Dnmt3a/b*, *Notch1*, *Mapk14*, and calcium channel subunits. Based on gene network analysis, interesting interactions among ribosomal, MAPK (mitogen-activated protein kinase), and glutamatergic pathway genes were also observed. Furthermore, enriched Elk1 transcription factor binding sites were identified within the DMR, and a differential non-CpG methylation dysregulated the Wnt pathway genes. The authors focused on the significant impact of early-life stress (ELS), particularly through the MS model, on the epigenetic brain scenario and concluded that the observed reduced sucrose preference in rats subjected to MS serves as a compelling indicator of anhedonia.

As demonstrated by Francis *et al.* (1), ELS may significantly impact brain development and functions (2,3). However, the complex ELS-mediated epigenetic modifications need to be carefully investigated to understand in a detailed manner the altered neurobiological pathways and illness trajectories related to stress-related conditions.

While most existing studies have documented the prevalence of DNA methylation changes at both CpG and non-CpG sites (4), Francis *et al.* (1) found directly an enrichment of Elk1 transcription factor binding sites within the DMR. In addition, these researchers reported that differential non-CpG methylation, specifically at CHH sites, dysregulated the Wnt pathway genes. Although Francis *et al.* (1) focused on ELS-mediated epigenetic modifications and postulated a generally comprehensive reprogramming of the genomic arrangement due to stress, a more careful delineation of both direct and indirect effects associated with methylation patterns is absolutely required.

Another criticism needs to be mentioned. While available evidence [including the study of Francis *et al.* (1)] is focused on hypermethylation rather than hypomethylation, particularly at CpG sites, how these changes may inhibit gene expression critically associated with brain development and stress response needs to be more clearly investigated. Although the enrichment of differentially methylated genes in pathways involved in synaptic function and brain development has been hypothesized (5), how and to what extent ELS may disrupt critically relevant biological pathways affecting brain development and neural functions is still poorly understood.

Moreover, according to Francis *et al.* (1), after MS, more than 33,000 DMCs and 151 DMRs were reported in the PFC of rats; however, how these changes need to occur in the PFC rather than in other brain regions is a matter of debate. While specific results have been reported with respect to specific brain regions, the patterns of epigenetic dysregulation may vary across different brain regions. We cannot ignore that the identification of specific DMRs, although located within gene bodies, is only an indicator of negative functional implications that are related to gene expression regulation. Based on the results of Francis *et al.* (1), ELS-induced modifications are supposed to be of paramount importance given their implications in the disruption of crucial cellular processes, but the profound implications of the methylation patterns in the emergence and maintenance of stress-related disorders are largely unknown.

Recent evidence (1) showed that the dynamic methylation of specific promoters is linked to reduced gene expression, but the specific dysregulated mechanisms related to differentially methylated genes are poorly understood. Francis *et al.* (1) stressed the involvement and implications related to specific methylated genes (e.g., *Dnmt3a/b*, *Notch1*, *Mapk14*, and calcium channel subunits). There is important evidence in the current scientific literature suggesting the key role of altered gene methylation patterns in neurodevelopment and stress response. The hypomethylated promoter of the *Notch1* gene in MS has been reported to be critically involved in neural development and neuropsychiatric disorders (6). Additionally, under hypomethylation conditions, glial glutamate transporter protein levels and uptake activity were found to be abnormally increased, suggesting that the existence of a dynamic DNA methylation program triggered by glutamate in glial cells modulates glutamate removal (7). Moreover, blood messenger RNA levels of GRIN3B, a glutamate ionotropic receptor NMDA type subunit-3B, was reported to be involved in the emergence and development of posttraumatic stress disorder. Furthermore, the hyper-DMCs in promoters regulating motor proteins

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and mutated genes linked to aberrant axonal transport and dysregulations of synaptic plasticity, neuronal function, learning, and memory have been observed in neurodegenerative diseases (e.g., Alzheimer's disease and Parkinson's disease). Finally, genes involved in synaptic signaling and neurotransmission seem to be specifically affected by epigenetic dysregulations such as histone H3K4 hypermethylation in the neuronal chromatin of the PFC in subjects with schizophrenia (8). However, it is not possible to exclude the possibility that even other key methylated genes as well as their multiple interactions may play a significant role in both the onset and maintenance of stress-related disorders. The profound and functional implications of the gene methylation patterns need to be investigated further, particularly based on the contrasting effect of gene body methylation on gene expression compared with promoters.

Francis *et al.* (1) documented reduced sucrose preference in rats subjected to MS, which serves as an important indicator of anhedonia. The observed methylation changes in transcription factor binding sites undoubtedly suggest a significant mechanism through which gene expression may be regulated in the context of brain development and behavioral alterations associated with MS; however, further additional mechanisms may exist and need to be elucidated in this specific regard.

Importantly, the detection of epigenetic modifications seems promising for further understanding the complex pathophysiology underlying major psychiatric conditions as well as potentially identify new therapeutic targets. Although the observed role of widespread alterations in genes that are critical for brain development, synaptic function, and stress response, occurring through methylation at both CpG and non-CpG sites in the promoter regions and gene bodies (9), cannot be ignored, the relevance of limitations/shortcomings in the study of Francis *et al.* (1) needs to be stressed, as comprehensively discussed by the researchers themselves.

First, under MS conditions, a variety of behavioral changes have been observed, while most of the recently published studies reported only subtle behavioral effects and long-lasting changes that need to be explored further and comprehensively replicated. Unfortunately, the lack of behavioral results may be related to abnormally lower sample sizes, which reduced the potential to identify differences in the forced swim and elevated plus maze tests (1). Furthermore, as suggested by Ding *et al.* (10), other epigenetic mechanisms (e.g., histone modifications, noncoding RNAs, RNA modifications, as well as chromatin remodeling factor) that were not investigated in the study of Francis *et al.* (1) may play an important role in stress-related disorders. Finally, the long-term and intergenerational effects of epigenetic modifications, which were not investigated in the study conducted by Francis *et al.* (1), need to be further explored given their implications in terms of effective treatments and innovative interventions in the field of stress-related conditions.

Therefore, future well-articulated studies should test the direct link between epigenetic changes and abnormally dysfunctional behaviors related to ELS and stress validated and replicated epigenetic changes to investigate the specific functional consequences on gene expression and behavioral alterations. Prospective longitudinal studies with robust methodologies will ultimately be needed to enable accurate comprehension of how individual, sociocultural, and psychological experiences are able to affect distinctive neural underpinnings of major psychiatric conditions.

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Article Information

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