Epigenetic Influences on Anxious and Depressive Behaviors: BDNF Links

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The identification of genetic biomarkers facilitates the staging of brain disorders, their prognosis, choice of treatments and interventions, prediction of response, and prognosis of outcomes over a wide spectrum of symptoms associated with affective states, possibly optimizing clinical practice treatments and procedures. In this regard, epigenetic mechanisms mediate the effects of the environment on human-animal neurodevelopment of behavioral repertoires and imply also that employing the sensitivity of laboratory animals to environmental cues may be applied usefully for the consideration of long-term health and welfare of individuals [26]. Epigenetic mechanisms regulating primary brain signals, e.g., serotonin, noradrenaline and hypothalamic-pituitary-adrenal axis functioning, as well as factors governing neurotransmitter metabolism seem implicated in the participation of neurotrophic factors that are indispensable for neurogenesis, survival, restoration and functional maintenance of ongoing brain systems, structurally and functionally [2]. The maladaptive response to stress-induced hypothalamic-pituitary-adrenal (HPA) axis dysregulation, over neurodevelopmental phases but most especially during early-life, consisting of exposure to glucocorticoids and stress in various forms, durations, and intensities gives rise to persistent epigenetic changes in the function of HPA axis-associated genes that govern homeostatic levels of glucocorticoids thereby focusing genes for brain-derived neurotrophic factor (BDNF) and tyrosine hydroxylase (TH) intimately involved in healthy and unhealthy affective conditions [6,19]. Greater levels of BDNF promoter methylation status, an emerging genetic biomarker for mood dysfunction, were associated significantly with a history of earlier suicidal attempt, suicidal ideation during treatment, and suicidal ideation during final evaluation in addition to higher Beck Scale for suicide ideation scores as well as poorer treatment outcomes for suicidal ideation [16]. Nevertheless, the influence of physical exercise as an intervention to alleviate symptoms and biomarkers of anxiety and depressiveness, accompanied by an increase in BDNF, has been shown to offer several benefits [1,27].

The case for epigenetic mechanisms underlying affective disorders, i.e. anxiety and depression, arising from permutations of early-life stress experience across the life span mediating the effects environmental regulation of the developing brain of both humans and laboratory animals attests to the plasticity of neurobiological pathways regulating stress responsivity, anxiety, depressive states, neurocognition, and other behaviors linked to quality-of-life has been established for the prenatal-postnatal-childhood and even adolescent period [4,9,12]. These conditions are maintained into adulthood, thereby implicating a lifelong lasting sensitivity and susceptibility to the pressures of environmental agents [14]. Kundakovic et al. [17], studied the influence exerted by postnatal maternal-separation upon mouse development by measuring parameters of behavioral, brain gene expression, and epigenetic alterations forth coming among the offspring of those mothers through the use of two different mouse strains, C57BL/6j and Balb/c, with both male and female offspring to study strain- and/or gender-associated differential response to maternal-separation. They obtained strain-specific and gender-dependent effects of maternal-separation during early adolescence upon estimations of open-field exploration, sucrose preference, and social behavior with analysis of cortical and hippocampal mRNA levels of the glucocorticoid receptor (Nr3c1) and Bdnf genes showing reduced hippocampal Bdnf expression in maternally-separated C57BL/6j females and elevated cortical BDNF expression in maternally-separated male and female Balb/c offspring. Their results from Nr3c1 and Bdnf (IV and IX) CpG methylation analyses demonstrated increased hippocampal Nr3c1 methylation in maternally-separated C57BL/6j males and elevated hippocampal Bdnf IX methylation in male and female maternally-separated Balb/c mice. Neurobehavioral and epigenetic outcomes appear to be regulated by the forces of interactive progressions of early-life adversity, genetic background and gender that implicate dynamic epigenetic alterations consisting of molecular modifications that alter gene expression without altering the underlying DNA sequence that elicit the type of detrimental plasticity observed in behavioral outcomes. The associations between the experience of prenatal stress, maternal separation, maternal care, abusive care giving in infancy and early childhood, juvenile social conditions, nutrition and housing, as well as adult social conditions are inevitably maintained into adulthood, thereby contributing significantly to the susceptibility of the offspring to subsequent stress exposure.
stress/truma and variation in DNA methylation and histone modification. Furthermore [18], have observed that serum Bdnf DNA-methylation presents a useful predictor of brain BDNF DNA-methylation and gene expression together with indications of behavioral vulnerability arising from early-life environmental conditions. Prevailing Bdnf expression and DNA-methylation changes linked to neuropsychiatric disorders have been the outcome of early-life adversity that emerge as expressions of depressive states and anxiety, schizophrenia spectrum disorder, bipolar disorder, and even autism. Notably, serum Bdnf DNA-methylation presents a novel biomarker for the early detection of psychopathology.

The associations between gastrointestinal visceras and human emotions have been noted with regard to inflammatory pressures upon affective states [20], for example, early adverse life events are linked with regional thinning of the cingulate cortex which is a brain region implicated in mood and negative affect disorders [8], with childhood maltreatment leading to exaggerated inflammatory response to acute stress challenges and induction of pro-inflammatory cytokine production. Thus, [6] observed that moderate-severe childhood maltreatment expressed in childhood trauma scores were correlated positively with overall changes in IL-6 response, a pro-inflammatory cytokine, as well as the maximum IL-6 concentration during the social stress test with higher levels of acutely released IL-6 and greater IL-6 concentrations over the study course as shown by the childhood maltreatment group in comparison with the control group. In this regard, an interactive association between polymorphisms related to stress experiences and inflammation and early adverse life events in modulating a key region of the emotion arousal circuit has been demonstrated [15]. Anxiety is associated with elevated levels of the inflammatory cytokines, such as interleukin-6 (IL-6), and an increased risk for defined by an inflammatory pathophysiology [11,24,28]. It has been shown that the expressions of epigenetic enzymes DNMT1 and Enhancer of Zeste Homolog 2 and interleukin genes were enhanced in anxious individuals scoring high on the Hospital Anxiety and Depression Scale-Anxiety [23]; IL-6 gene expression was correlated strongly with DNMT1, elevated expressions of DNMT1, HDAC1, and HDAC2, and reduced expression of AChK14 in the hippocampus in comparison with the offspring from non-stressed dams. The data from MeDIP and ChIP analysis exhibited elevations of methylation but reductions of binding of AChK14 upon specific BDNF promoters. Additionally, the depressive-like mouse mutant, ‘mor1 knockout’, shows an up-regulation of total Bdnf mRNA-levels in the hippocampus [25].

In conclusion, there appears to be a strong case for the notion that early-life adversities, particularly referring to prenatal stress, through the mediation of epigenetic alterations [3], exerts immense, far-reaching and enduring manifestations upon psychiatric health and well-being during later life, that are more profound than those exerted postnatally, or during childhood or adolescence or early adulthood. In this context, there exists a sufficiency of evidence that aberrant epigenetic mechanisms, particularly related to DNA methylation, in the brains of ‘small-for-gestational-age’ and ‘large-for-gestational-age’ offspring are linked to later expressions of anxiety and depression, with outcomes relating to disruptions in the cell cycle during development and gene expressions in adolescence and adulthood [13].

REFERENCES
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