MIND AS EPIGENETIC MODIFIER IN MOOD DISORDERS

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Abstract
Epigenetic modifications of DNA might be crucial for understanding the molecular basis of mood disorders. One reason for this is that epigenetic factors are sometimes plastic enough to react the external and internal environments. New scientific studies suggest, that these environmental factors can be not only food or chemicals, but also spiritual: positive emotional state, optimism, reaction to stress. The aim of this manuscript is to provide a conceptual background for studies by reviewing key findings from different forms of investigation. In order to provide an understanding the role of genetic and environmental (spiritual) factors in the causation of mental disorders here is a simplified account of some of the key features of how genes ‘work’. Results of that review indicate that of particular interest, traumatic events or negative mind content may potentially alter our DNA methylation pattern and induce abnormal brain gene expression and ultimately depression, and other mood disorders. In summary, this review demonstrates that an epigenetic state of a genes responsible for mental health can be established through life experience and thinking manner and is potentially reversible.

INTRODUCTION
The human genome project has given us a more nuanced understanding of how genes work [1]. It is now clear that they are not static blueprints that dictate our biological behavior [1-3]. In recent years, epigenetics have been studied as a possible mechanism that underlies psychopathologies [1, 4-7]. Epigenetics (literally “above genetics”) is defined as chemical modifications of DNA that alter its structure and function [8]. These modifications consist of either methylation of the DNA itself, or of several chemical modifications of the histones (proteins which bind DNA and help determine its structural conformation) [9-11]. These modifications change the expression pattern of the gene, without changing the gene sequence itself. Most genes have switches, called promoters that control how, when, and even if they become active, a phenomenon known as gene expression [12-14]. Other regulatory elements, called gene enhancers, also play a role. Even slight alterations in promoters or enhancers can lead to dramatic changes in gene expression [15]. The “epigenetic hypothesis” of depression, states that faulty of expression of important genes in the brain are occurring because of abnormal modifications to the DNA sequence [16,17]. These abnormal modifications may be randomly occurring, or may be driven by environmental effects, such as life style and content of thoughts [14, 18-20]. Recent scientific studies determined that humans that had experienced child abuse, and then committed suicide in their adulthood, had abnormal DNA methylation in a gene that controls our response to stress and trauma. Numerous studies in animal models have also suggested that lifetime experiences may alter our DNA’s structure in the brain, and therefore lead to mood disorders [16, 21]. Genetic systems and nervous systems are dynamic (cybernetic) in contrast to previous conceptualizations with genes and brains fixed in form and function [21, 22]. Questions of nature versus nurture are meaningless, and we must turn to epigenetics—the way in which biology and experience work together to enhance adaptation throughout thick and thin. Defining endophenotypes—road markers that bring us closer to the biological origins of the developmental journey—facilitates our understanding of adaptive or maladaptive processes. For human mood disorders such as depression and bipolar disorder, the inherent plasticity of the nervous system requires a systems approach to incorporate all of the myriad epigenetic factors that can influence such outcomes [23, 24].

The aim of the article: to provide a conceptual background for studies by reviewing key findings from different forms of investigation about the role of genetic and spiritual factors in the development of mood disorders.
**SOURCES AND WORK METHODS**

This paper will selectively summarize what is currently known about epigenetics, wave genetics and spirituality. A search was conducted using PubMed, Scopus and Scholar google from 1990 through 2011 using the search terms epigenetics, genes, mind, spirituality, mood disorders, prevention. The search was limited to articles published in the English language. Some nonpublished studies which were presented in conferences were quoted in view of their importance.

**RESULTS**

Early emotional experience can alter behavior and physiology. These effects are, in part, mediated by sustained alterations in gene expression in selected brain regions. The critical question concerns the mechanism of these environmental “programming” effects. This is proven with an animal model that studies the consequences of variations in mother-infant interactions on the development of individual differences in behavioral and endocrine responses to stress in adulthood [12]. A number of variants in candidate genes have been implicated in contributing to maladaptive and resilient responses that underlie alterations in neuronal plasticity and subsequent behavioral mood disorders, especially depression [26]. Evidence is strongest for genes involved in reaction to stress (corticotrophin-releasing hormone [CRH]; glucocorticoid receptor [GR]), regulatory neurotransmitters, and receptors (serotonin 5-HTTLPR), neurotrophic factors, nuclear factor-kappaB and transcription factors [27]. Studies of the CRH-1 gene in humans, for example, have shown that specific variants are associated with differential hormonal responses to stress, and with differing rates of depression and suicidal behavior [28]. Increasingly, such genetic effects have themselves been found to be modulated by individual variation in environmental context and history (gene x psychological environment, GxE) [29]. Epigenetics, which focuses on non-genomic alterations of gene expression, provides a mechanism for understanding such findings, through alteration of DNA methylation and subsequent silencing of gene expression or through physical changes in DNA packaging into histones [30]. A comprehensive review of this literature is beyond the scope of this article, but the findings of selective recent studies in these areas are illustrative of the regulatory complexity that influences the possible translation of stressful experiences into depression.

**The early life social environment and epigenetics.** New findings demonstrate that the structural modifications of the DNA can be established through environmental programming and that, in spite of the inherent stability of this epigenomic marker, it is dynamic and potentially reversible [29, 31, 44]. Augmented maternal care was associated with reduced hypothalamic response to stress in rat pups and altered expression of CRH into adulthood [32]. Suggestive human data compatible with these mechanisms have been reported [33, 34]. Oberlander et al. [35] for example, found that prenatal exposure to third trimester maternal depression was associated with increased methylation of the glucocorticoid receptor gene at 3 months of age in the newborn child, while McGowan [29] reported decreased levels of GR expression in the hippocampus of suicide victims with a history of childhood abuse, in comparison with those without such history and to controls. Tyrka and colleagues [36] have also shown that variants in the CRH1 receptor gene appear to interact with a history of childhood abuse in determining cortical response to CRH. A separate body of research has focused on genetic investigations in components of serotonergic function, most commonly on a variant in the serotonin promoter (5HTTLPR), and, to a lesser extent, on serotonin receptor genes [37]. In a small-scale study that remains controversial, Caspi et al. [38] showed that the effect of a variant in 5HTTLPR on increasing risk of depression was dependent upon a history of previous life stresses; several large-scale attempts at replication failed to support these conclusions and subsequent meta-analyses have been both positive and negative [39, 40]. Ressler et al. [41] have suggested that gene x gene x environment interactions may be involved, and reported that 5-HTTLPR alleles interacted with CRH1 haplotypes and child abuse history in predicting depressive symptoms.

Similar to the rat and human, the changes in DNA methylation associated with differences in rearing in monkeys are widespread in the genome, that they are not limited to the brain and occur in T cells as well [45, 46]. Signature of DNA methylation is associated with early life adversity [46] supporting the hypothesis that social environment DNA methylation signatures are found system wide and could be examined in peripheral blood cells. Other studies have also demonstrated that epigenetic effects associated with behavioral adversity could be detected not only in brain cells, but also in blood cells. The NR3C1 promoter was more methylated in lymphocytes in newborns exposed prenatally to maternal depression than control newborns [47]. Pituitary adenylate cyclase-activating polypeptide (PACAP), a protein known to be involved in stress response in the pituitary was found to be differentially methylated in peripheral blood cells in humans with post traumatic stress syndrome [48]. A long line of data have established that the physiological response to early life socio-economic adversity is not limited to the brain [49, 50]. There is no reason therefore
to believe that DNA methylation changes in response to adversity should not occur in the periphery as well as the brain. Hippocampal GR gene expression, like all genes, is controlled by the epigenome, which is comprised of DNA methylation [52] and chromatin structure, including histones and their modifications [53]. The effect of maternal care is remarkably specific, with highly significant alterations in the methylation status. Thus an epigenomic state of a gene can be established through behavioral programming, and it is potentially reversible [54].

**Wave genetics and health.** Complex information can be encoded in electromagnetic (EM) fields, as we all know from coding and decoding of television and radio signals. Even more complex information can be encoded in holographic images. DNA also can act as a holographic projector of acoustic and EM information which contains the informational quintessence of the biohologram [27]. Only 3% of human DNA encodes the physical body. The remaining 97% of the 3 billion base pair genome contains over a million genetic structures called transposons, that have the capacity to jump from one chromosomal location to another [19, 37]. A model of the mind-body relationship is developed in which novel biophysical principles in genome function generate a dynamic possessing attributes consistent with both our psychophysical nature and consciousness. The Gariaev group has proposed a theory of the Wave-based Genome where the DNA-wave functions as a Biocomputer. They suggest (1) that there are genetic “texts”, similar to natural context-dependent texts in human language; (2) that the chromosome apparatus acts simultaneously both as a source and receiver of these genetic texts, respectively decoding and encoding them; (3) that the chromosome continuum acts like a dynamical holographic grating, which displays or transduces weak laser light and solitonic electro-acoustic fields [42].

The distribution of the character frequency in genetic texts is fractal, so the nucleotides of DNA molecules are able to form holographic pre-images of biostuctures. This process of “reading and writing” the very matter of our being manifests from the genome’s associative holographic memory in conjunction with its quantum nonlocality [27]. The same researchers suspect the ability of chromosomes to transform their own genetic-sign laser radiations into broadband genetic-sign radio waves. The polarizations of chromosome laser photons are connected nonlocally and coherently to polarizations of radio waves [27, 42]. K. Pribram postulated a neural hologram made by the interaction of waves in the cortex, which in turn is based on a hologram of much shorter wavelengths formed by the wave interactions on the sub-atomic level [43]. Endogenous DMT (N,N-dimethyltryptamine), that primary source is glandula pinealis, described as the source of visionary light in transpersonal experiences. DMT production is particularly stimulated, according to Strassman in the extraordinary conditions of birth, sexual ecstasy, childbirth, extreme physical stress as well as meditation [47]. Pinal DMT also plays a significant role in dream consciousness. Creative, novel and enriching psychotherapeutic experiences can lead to neurogenesis, gene expression, and healing which facilitate mind-body communication and can have a long-term transformative effect on the whole person [52]. Thus, bioholography has relevant applications for optimizing health, well-being and even self-realization. It is relevant in biophysics, medicine, psychobiology, psychotherapy and the holistic healing arts. Meditative techniques using sound, sight, or the mind may generate particular wave patterns whose fields induce resonance in the brain. Millennia of human trial and error have determined that certain “sacred” words, visual images, and mental exercises exert uniquely desired effects. Such effects may occur because of the specific fields they generate within the brain. These fields cause multiple systems to vibrate at certain frequencies [47, 69].

The biohologram model of human-beeing forms at the moment of conception. Researchers have found that at the moment of ovulation there is a definite shift in the electrical fields of the body of the woman [27]. The membrane in the follicle bursts and the egg passes down the fallopian tube. The sperm is negative with respect to the egg. When the sperm and egg unite, the membrane around the egg becomes hyperpolarized, shutting out other sperm. It is at this moment that the electromagnetic entity is formed. The fertilized egg cell contains all the information necessary to create a complete operational human being [42]. In the quantum holographic DNA-wave biocomputer theory, DNA is a self-calibrating antenna working by phase conjugate adaptive resonance capable of both receiving and transmitting quantum holographic information stored in the form of diffraction patterns -- quantum holograms [43, 53].

**Psychogenetic creativity hypothesis.** Enriching life experiences that evoke psychobiological arousal with positive fascination and focused attention during creative moments of art, music, dance, drama, humor, spirituality, joy, expectation, and social rituals can evoke immediate early gene protein cascades to optimize brain growth, mind-body communication, and healing [51, 52, 69]. The psychotherapeutic approach can contribute to psychobiological arousal, enrichment and relaxation; it may be possible to help people find optimal levels of mental stimulation to facilitate actual growth in the hippocampus of their brain.
to encode new memory, learning and behavior optimizing psychobiological growth and healing. E. Rossi describes a mind-body communication channel that is pertinent in that it may describe another way neural plasticity and healing manifests from REM [52]. He describes how immediate-early genes (also called “Primary Response Genes” or third messengers) play a central role in the dynamics of waking, sleeping, dreaming, and mind-body healing at the cellular level. There is evidence that immediate-early genes (IEGs) function as mediators of information transduction between psychological experience, behavioral states, and gene expression. A wide range of behavioral state-related gene expression (from relaxation, hypnosis and sleep to high arousal, performance, stress and trauma) culminate in the production of new proteins or homeostasis, physical and psychosocial adaptation [69]. Behavioral states modulate certain patterns of gene expression. Interaction between the genetic and behavioral levels is a two way street. Genes and behavior are related in cybernetic loops of mind-body communication. A look at the systems related to IEGs, shows that they affect all the systems disrupted in bipolar disorder. They are expressed continually in response to hormone messenger molecules mediating processes of adaptation to extracellular signals and extracellular stimuli, that come from the outside environment, including temperature, food, sexual cues, psychosocial stress, physical trauma, and toxins [52].

**DISCUSSION**

Around fifty years ago, tricyclic antidepressants were introduced as an effective treatment to battle clinical depression. These drugs work by increasing the extracellular concentrations of various chemicals in the brain, including serotonin [55]. Nonetheless, after many years extensive studies, the “serotonin hypothesis” still does not seem to explain completely the basis for clinical depression. First of all, there is little evidence of substandard serotonin neurotransmission in patients with depression. Secondly, there is still a significant portion of patients with clinical depression that are resistant to anti-depressants that modulate serotonin, including SSRIs. In addition, the effects of these medications often wear off after long treatment regimens. Therefore, the molecular basis underlying depression has, until now, still been undetermined [56]. Diabetes, heart disease, even lung function are impacted by external factors like nutrition, exercise, and pollution exposure. But mental health is part of the epigenetic picture as well: chronic stress and even early emotional experiences, it turns out, may be significant enough to alter our genes’ expression [20]. Depression, because of its duration and slow response to medication, has been an intriguing area for epigenetic research. Researches found that chronic social stress can cause chromatin changes in genes in the brain’s nucleus accumbens and hippocampus [57, 58]; they have observed that chemical alterations of DNA are dynamically regulated from the perinatal period to old age. In animal models of chronic stress, scientists were able to manipulate specific brain areas in ways that produced antidepressant-like effects. That’s the effect of epigenetics. Thus we have more influence on our mental and physical health than we previously thought. While we can’t control every aspect of our environment or our emotional experiences, we have the considerable potential to ameliorate those factors. In terms of physical health, we can eat well, supplement wisely, exercise strategically, sleep adequately, and reduce our exposure to toxins as much as possible. For our mental health, we can do all of the above as well as learn effective ways to cope with the stress in our lives (as well as find overall fulfillment) [59-61]. While physical activity can help us feel less stressed in the short term, a personally beneficial meditation practice (yoga, Tai Chi, Transcendental, etc.) can fundamentally change gene expression and our response to stress [62-69]. Over time, our efforts can potentially modify the expression of those genes that are involved in stress response and very likely related areas of mental health like anxiety and depression [70-73]. While some of us might be more genetically predisposed to certain physical and mental health conditions, epigenetics offers hope that our own choices and practices can play a significant role in their prevention and treatment. Furthermore novel experiments were performed by Luc Montagnier (who shared the Nobel Prize for Medicine in 2008 for his part in establishing that HIV causes AIDS). He performed experiments, that show that DNA can send spooky electromagnetic imprints of itself into distant cells and fluids [74]. Physicists in Montagnier’s team suggest that DNA emits low-frequency electromagnetic waves which imprint the structure of the molecule onto the water. Every thought has influence on electroencephalogram (EEG). So content of mind may have influence on electromagnetic origin of DNA and it's expression [75]. Creative, novel and enriching psychotherapeutic experiences can lead to neurogenesis, gene expression, and healing which facilitate mind-body communication and can have a long-term transformative effect on the whole person [27, 52]. Thus, bioholography has relevant applications for optimizing health, well-being and even self-realization. It is relevant in biophysics, medicine, psychobiology, psychotherapy and the holistic healing arts [53]. All these findings demonstrate that a change in mental conditioning not only
affects gene expression, but also can actually change the way our genes operate [20,69]. They prove that our genes no longer should be thought of as immutable determinants of our fate, but as dynamic entities, switching on and off in response to outside influences, as much the result as the cause of our mental, emotional, and biological processes [76-77]. Multiple findings indicate that psychoeducation at epigenetic level is effective and may prevent mood disorders or improve functioning in depression, highlighting the need for “mind hygiene” [78-79]. People with a strong motivation to live healthier must understand that they take responsibility for their mind content and for lives instead of being victims of events. Each and every patient has the resources within to affect mental health and prevent the development of depression.

CONCLUSION

The scope of involvement of epigenetic modification in long-lasting regulation of genome function is wider than has originally been thought. Epigenetic DNA methylation acts as a mechanism for providing differential identities to similar DNA sequences. Multiple data in both animals and humans support hypothesis that DNA methylation can act as a mechanism for adaptation of the genome to different psychological environments. The studies presented in this review provide support for the effect of thinking manner and behavior on brain functions that are responsible for the development of mood disorders and that these effects are rendered permanent throughout life by epigenomic reprogramming. These data highlight the importance of spirituality and personal responsibility of mind content required for mood disorders prevention at genetic and epigenetic level.

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