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# Implications of Epigenetic Mechanisms in the Development and Treatment of Personality Disorders

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Epigenetics deals with the genic expression processes that do not involve modifications of the DNA sequence, that is, focuses on the different trajectories of a given genotype throughout the organism's lifespan. These processes are involved in basic biological functions such as the cellular differentiation or sexual selection, in the development of complex diseases such as Rett's syndrome and in psychiatric disorders such as schizophrenia and depression among others. Epigenetic studies are yielding evidence that environmental events and psychosocial factors can modify the epigenome. This work reviews studies analyzing the influence of environmental factors involved in the pathogenesis of behavioral features and phenotypic expression of personality disorder's symptomatic domains, such as late onset affective symptoms related with early adverse events in childhood and dysfunction of stress modulation mechanisms. In addition, the knowledge of these epigenetic mechanisms may contribute to the identification of novel both psychotherapeutic and pharmacological therapeutic targets for the treatment of personality disorders.

Keywords: Epigenetics, Methylation, Histones, Personality disorders, Stress

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## Implicaciones de los mecanismos epigenéticos en el desarrollo y tratamiento de los trastornos de la personalidad

La epigenética estudia los procesos de expresión génica que no requieren de la modificación de la secuencia de ADN, es decir, se ocupa de las diferentes trayectorias que un genotipo puede tomar a lo largo del desarrollo del organismo. Estos mecanismos están implicados en procesos biológicos básicos como la diferenciación celular o la selección sexual, en el desarrollo de enfermedades complejas como el síndrome de Rett y en trastornos psiquiátricos como la esquizofrenia y la depresión, entre otros. Los estudios epigenéticos están proporcionando evidencias de que los eventos ambientales y los factores psicosociales pueden modificar el epigenoma. En este trabajo se revisan los estudios que analizan la influencia de eventos ambientales implicados en la patogénesis de rasgos de conducta y en la expresión fenotípica de dominios sintomáticos propios de los trastornos de la personalidad, como la sintomatología afectiva diferida tras acontecimientos adversos en la infancia y las alteraciones en la modulación del estrés. Además, el conocimiento de estos mecanismos epigenéticos puede contribuir a la identificación de nuevas dianas terapéuticas, tanto farmacológicas como psicoterapéuticas, en el tratamiento de los trastornos de personalidad.

Palabras clave: Epigenética, Metilación, Histonas, Trastornos de la personalidad, Estrés

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## INTRODUCTION

It is currently accepted from the neuroscientific point of view that human behavior is the result of interaction between three factors: a) genetic endowment of the organism, b) experiences accumulated by the organism, the influences of environmental events on the genetic heritage and c) perception of the subject of a given situation. This view has been fostered by the contributions of genetics to the study of the personality.<sup>1</sup> Furthermore, knowledge derived from the theory of evolution have strengthened the idea that the brain structure is modified through the natural selection process and that the genomic variation is united to different levels of risk of psychopathology. However, in the last decade, genetic research has taken a new leap on providing a more dynamic and modifiable vision of the genome, which is permanently regulated by environmental stimuli. This control is called epigenetic regulation and determines how the physical and social environment can cause changes in molecular structures that intermediate in the expression of the genes and how these changes can even be transmitted intergenerationally.<sup>2</sup>

This work examines several studies that analyze the influence of environmental events on the gene regulation mechanism, with special attention to the consequences of this interaction on the conformation of the nervous system, personality traits and personality alterations.

### Epigenetics and epigenetic mechanisms

The term epigenetics was coined by the genetist Conrad Waddington<sup>3</sup> to define the study of the interactions between the genotype and phenotype, that is, between the coded information in the genes and that which is really expressed. Epigenetics studies the gene expression processes that do not require modification of the DNA sequence, in other words, without altering the reading of the nitrogenous bases of adenine, thymine, cytosine and guanine. The sequential order of these molecules in the coding regions of the genome determines the chemical nature of the proteins that are coded by the genes and consequently their function. These processes may act over the lifetime of the organism. From a neuronal point of view, recent proposals have defined epigenetics as the "the structural adaptation of chromosomal regions so as to register, signal or perpetuate altered activity states."<sup>4</sup> Finally, epigenetics represents the different pathways that a genotype may take during the development of the organism.<sup>5</sup> Currently, two main mechanisms of epigenetic regulation have been identified (Figure 1).<sup>6,7</sup>

a) DNA methylation: This phenomenon is produced by adding a methyl group to the cytosine-guanine base pairs in the gene promoter group. In most of the cases, the consequence of the DNA methylation is less

expression of the gene or "gene silencing," while less methylation is generally associated to greater activation in the gene transcription.

b) Histone modification. Histones are globular proteins around which the DNA recurrently winds. The DNA+histone complex is called *nucleosome* and the nucleosomal cluster is called *chromatin*, which, in turn, shapes the chromosomes. A series of chemical phenomena (called acetylation, methylation, ubiquitination or phosphorylation, and carried out by histone modifying proteins as the acetyltransferases, deacetylases or methyltransferase enzymes) that affect the positioning of the histones are capable of altering the chromatin structure, making it accessible or inaccessible to the transcription factors and consequently modify the gene expression. For example and in general, histone acetylation opens the chromatin to the transcription factors and promotes activation of the gene function and deacetylation determines the compacting of the chromatin and silencing of the gene activity.

### Epigenetics, basic biological processes and disease

Epigenetic mechanisms play a fundamental role in many basic biological processes for the development of the organism as, for example, in the cellular differentiation processes. All the body cells have the same genome although they have different functions and diverse structures. The epigenetic marks determine which genes are activated and silenced in each cell, thus giving it a specific and differentiated nature (giving rise to a neuron or to an hepatic cell, for example). In addition, silencing of Chromosome X in men also has an epigenetic nature. It has also been demonstrated that the differences observed through ontogenetic development in the phenotype of monozygotic twins, who in the beginning share the same genotype, are due to different patterns of DNA methylation and histone acetylation that occur during development.<sup>8</sup> Regarding neuronal function, the epigenetic plays an important role in cell differentiation in the neurodevelopment, in maintenance of circadian rhythms, in mediation of synaptic activity induced changes in electroconvulsive therapy of depression, in the formation of mnesic content and in synaptic plasticity.<sup>9</sup> It has also been observed that the capacity for learning and formation of experiential memory is associated with rapid and transient changes of DNA methylation in the hippocampus (in the case of associative learning and fear memory) and with modification of histones in the prefrontal cortex (in the case of conditional fear after extinction).<sup>10</sup>

On the other hand, recent studies are providing evidence of the involvement of epigenetic processes in the de-

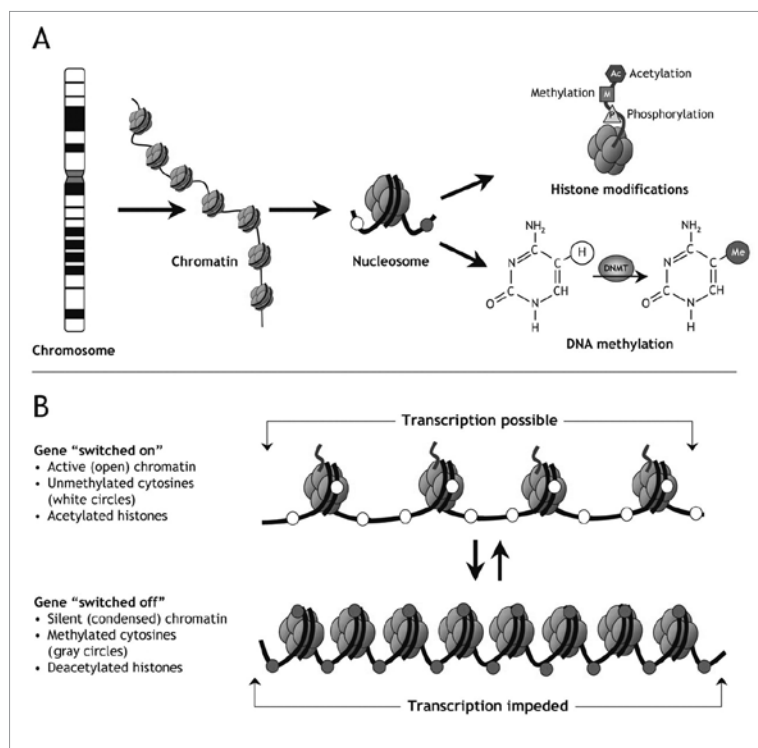
velopment of behavioral phenotypes in different psychiatric disorders such as schizophrenia, depression, drug addiction and anxiety disorders.<sup>11-14</sup> In addition, a significant epigenetic contribution has been found in other complex disorders such as the Rubinstein-Taybi syndrome, Rett syndrome, Fragile X syndrome and Alzheimer's disease.<sup>9</sup> In the case of depression, a relation modulated by epigenetic mechanisms, between the decrease in BDNF gene expression and the pathophysiology of depression has been proposed. Specifically, it has been found that early adverse events are associated with stable changes in BDNF transcription and the latter in turn leads to less expression of mRNA and proteins in the prefrontal cortex, amygdala and hippocampus.<sup>15</sup> These results have been observed associated to greater depression, anxiety and reactivity to stress in adolescence and adult life.

In summary, one of the most relevant contributions of epigenetics is the statement that the chromatin-modifying proteins are sensitive to environmental signals, so that the DNA and histones may be marked based on environmental events. In this way, it has been observed that the epigenome can change based on nutrition,<sup>16</sup> drug consumption,<sup>17</sup> exercise<sup>18</sup> and learning.<sup>19</sup>

## EPIGENETICS, BEHAVIOR AND PERSONALITY

### Epigenetic mechanisms in the makeup of behavioral traits

Epigenetic research on behavior is accumulating growing evidence indicating the importance of gene-environment interaction in the makeup of behavioral traits. Within the contexts of animal research, it has been observed that the type of maternal cares during the postnatal period modifies the epigenome of the glucocorticoid receptor in the hippocampus of rat pups and that these changes are associated to different levels of response to stress.<sup>20</sup> In one work that was a significant milestone in epigenetic research of animal behavior, Weaver and his team observed that the pups receiving better maternal cares (grooming and licking by the mother) had less methylation of the glucocorticoid receptor in the hippocampus, independently of the genotype inherited. This lower methylation produces greater expression of the glucocorticoid receptor, which attenuates the response to stress of the hypothalamic-pituitary-adrenal (HPA) axis. Therefore, the rats receiving better care in early age have less response to stress and less tendency to anxiety.



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Figure 1

Diagram of the principal epigenetic mechanisms: (a) modification of histones and DNA methylation and (b) changes in the chromatin position that determine the gene transcription

Response to stress of the HPA axis has also been studied in human samples, this response being related with environment events in early childhood. Thus, for example, in subjects with a history of childhood maltreatment, it was found that having suffered sexual abuse is associated with greater methylation of the glucocorticoid receptor gene promoter and that the severity of the abuse has a positive correlation with the grade of gene methylation.<sup>21</sup> Other studies have found similar results, although without analyzing the epigenetic mediators: for example, it has been found that healthy adults who state they had worse maternal care in their infancy have greater concentration of cortisol in saliva and greater dopamine release when there are stress-inducing stimuli.<sup>22</sup> These data agree with the evidence of epigenetic changes (reduction of the methylation of specific cytosines with the regulatory regions of the CRF gene in the hypothalamus and amygdala, with increase of gene expression) that intermediates between prenatal stress and depression and sensitivity to stressful events in the adult life.<sup>10</sup>

Regarding the duration of the epigenetic effects, it has been found that the epigenetic marks can persist until adult age and affect vulnerability to psychopathology. Specifically, greater methylation of the glucocorticoid receptor was found in the brains of suicide victims who also had a history of childhood abuse compared to control subjects.<sup>23</sup> These findings suggest that certain suicides could be associated to childhood abuse through epigenetic mechanisms and that epigenetic marks established in childhood can last in the long term.

However, it has also been observed that in spite of the stability of the epigenomic marks, these are reversible over lifetime through the use of drugs and by exposure to different environmental events. One study that used adult rats with low response to stress and that received adequate maternal cares observed that the methionine infusion (methyl donor substance) reversed the glucocorticoid receptor methylation pattern in the hippocampus associated to low response to stress and increased reactivity of the HPA axis to the stressful stimuli.<sup>24</sup> Furthermore, administration of DNA methyltransferase inhibitors as zebularine, 5-aza-deoxycytidine or RG-108 produces an effect of inhibition of learning of the response of conditioned freezing.<sup>4</sup> It has also been found that valproic acid, widely used as anticonvulsant and mood stabilizer, consolidates learning of fear extinction conditioned through its inhibitor effect of histone deacetylation in the BDNF in the prefrontal cortex.<sup>25</sup>

Along the same line of investigation, the effect that environmental enrichment, understood as exposure to new environments, more complex social interactions or the voluntary performance of physical exercise, produces on epigenome and behavior, has been evaluated. It was observed that physical exercise induces activation of histone

H3 phosphorylation in the hippocampus and C-Fos gene which permits better stress coping strategy in laboratory animals.<sup>26</sup> The intervention of similar epigenetic mechanisms in other studies performed in humans, where it was found that regular aerobic exercise induces plasticity in the hippocampus with an increase in volume both in healthy subjects as well as those with schizophrenia, could be hypothesized.<sup>27</sup> It has also been observed that rat pups receiving low maternal cares modified their behavior towards that of having received high cares after being exposed to an enriched environment<sup>28</sup> and rats who were subjected to maternal separation and developed high reactivity on the HPA axis to stress compensated this response after through more favorable rearing conditions (larger cages, more toys in different places and more relations with peers).<sup>29</sup>

These results are in agreement with other studies which, although they did not analyze epigenetic mediators, found that environmental enrichment between three and five years of age in humans is associated with better response of psychophysiological activation in measurements related with maturation of cortical regions and data processing.<sup>30</sup> Along the same lines, animal models have proposed some epigenetic mechanisms as mediators of the beneficial effects of environmental enrichment: for example, a global increase of H3 and H4 histones in prefrontal cortex and hippocampus has been found associated to improvements in learning,<sup>31</sup> an increase of H3 histone phosphoacetylation of the hippocampus related with lower stress response and better cognitive performance,<sup>26</sup> and induction of H3 histone trimethylation in the hippocampus BDNF.<sup>32</sup>

Given that one of the biological risk factors for antisocial disorder is autonomic hypoactivation, these results suggest that environmental enrichment in early childhood could have a beneficial effect in the prevention of development of antisocial personality traits.<sup>33</sup> Thus, this evidence suggests that rearing and educational style not only affects behavior and emotions of the child but also the development of the hormonal, neurophysiological response systems and the expression of the genotype.<sup>34</sup>

In summary, it seems that the epigenetic mechanisms are good candidates to understand the interaction between genes and environment, that is, the process by which environment interacts with the genome and produces individual differences in the expression of specific traits.

### Integration of epigenetics and personality: Depue model

On the other hand, some attempts have been made to develop models to explain personality that integrate epigenetic variables. One of the most developed approaches

is that of Depue,<sup>35</sup> that also includes a genetic and environmental approach as well as that of trade psychology. Given its extension, we are going to give a very brief summary of the principal aspects, with special attention to the epigenetic variables. In this model, Richard A. Depue proposes a dimensional approach of personality alterations that he conceives as the expression of extreme variants of basic traits of normal personality. The development of these extreme trait variants is the result of the interaction of three factors. First, the biological systems that underlie the trait. Second, the individual variations of said biological systems determined by genetic polymorphisms and finally, the influence of the environment events on the neurobiological systems through the action of epigenetic mechanisms.

The first trait and one of the best studied is neuroticism associated to functioning of three biological systems: corticotropin-releasing system, serotonergic system and its serotonin transporter polymorphisms, and glucocorticoid system. The function of these systems is to regulate fear behavior in the face of threatening stimuli and anxiety in the face of potential threats. The functionality in all of them is modified through the influence of adverse events in infancy. In this sense, animal research paradigms<sup>36,37</sup> have observed that rat pups receiving high maternal cares have a cascading series of neurobiological changes in the hippocampus that include: a) greater serotonin transmission, b) increase of histone acetylation, c) increase of glucocorticoid receptor gene and d) activation of neurotrophic factors (BDNF) that promote synaptogenesis in the hippocampus. It has also been found that the administration of histone deacetylation inhibitor in rats with elevated response to stress decreases said response, transforming their reaction as if they had been reared by mothers who provide high cares.

A critical aspect of these findings is the moment of evolutive development in which the environmental events occur, since the epigenetic processes could be "open" only in the first weeks of life in the rodents (perhaps the first months in primates). Therefore, critical periods in which experience interacts with development of prosencephalic regions that intervene significantly in anxiety response to environmental signals seem to exist.<sup>38</sup>

A second trait analyzed in this model is extraversion, understood as predisposition to approach positive stimuli of the environment, which produces incentive motivation. The biological base of this system is the combination of dopamine projections between nucleus accumbens and ventral tegmental area, a fundamental neural circuit for motivated behavior and for subjective feeling of pleasure for the reward. It has been observed that early stress induced in rodents and in monkeys entails:<sup>39</sup> a) sensitization of the dopamine pathways in the nucleus accumbens towards the presence of stressors in later periods of life, b) greater facility to introduce self-administration of drugs and c) significant

decrease of dopamine transporter in the accumbens. Although the epigenetic mediators of these changes have not been identified, it has been proposed that these phenomena can cause a more extreme position in the extraversion traits that favor activation of impulsive and histrionic behaviors, and whose consequence can lead to deterioration of the social adaptation of the subject.

Depue proposes that a third basic trait is social closeness, which orients the subject to maintain social relations with stable attachment in the long term and that is related with the functionality of the endogen opioid system, more specifically with the  $\mu$  receptor. However, he points out the absence of research on environment influences on the functionality of this neurotransmission system, although it is an accepted fact that attachment behavior is modulated through experiences of social interaction in the post-natal period.

The trait of sensitivity to social rejection pushes the subject towards avoiding the malaise caused by separation and it is aroused by group exclusion or threat of harm or loss of the relationships. Emotional response to these states of loss is emotional pain, which is at least partially controlled by the dorsal regional of the anterior cingulate cortex. In situations of social rejection, intense activation of the dorsal cingulate has been observed. This, in coordination with the amygdala, generates an unpleasant body sensation of emotional pain. Extreme values of this trait appear in dependent-borderline and avoidant type personalities. There are no research works on this trait that analyze epigenetic effects of the early experiences on the function of the dorsal cingulate, although it is recognized that said experiences affect the shaping of confidence of attachment relationship.

Finally, the last trait proposed by Depue is called "constraint" and reflexes a general dimension of self-regulation of impulsive behavior in which a certain threshold level is established for evoking an emotional, motor or cognitive response. This trait does not affect any emotional or motivational system specifically but affects the systems of motivated behavior, social closeness or tendency towards anxiety, modulating certain response thresholds to the stimuli pertinent to each system. Although the epigenetic mediators of this influence are not explained, it is known that the principal biological base of this trait is the serotonergic function, which has significant effect on emotional behavior, motivation, cognition, food intake, sexual behavior, etc.

In summary, these data highlight the biological value of experiences the subject is exposed to in infant life and those during his/her lifetime, on indicating that environment can shape the activation of genes determining from certain character traits to a specific psychopathological phenotype. According to this model, the presence of environmental

events can interact with genetic endowment of the individual to form a phenotypal expression with greater affective instability and negative emotionality, which can be accompanied by greater deterioration in the interpersonal relationships. Meta-analytic studies have indicated these three aspects as common characteristics of the personality disorders<sup>40</sup> and have also found genetic variables that contribute independently to each factor.<sup>41</sup>

## Epigenetic alterations in personality disorders

Studies on epigenetics in personality disorders (PD) are currently in an initial development phase. In the absence of empirical support from the classification of PD as discrete entities, the current consideration and that most mental disorders emerge based on a genetic vulnerability bestowed by multiple genes of small size of effect on which environmental factors interact are added.<sup>42</sup> However, this approach still has important limitations.<sup>43</sup> First, the causality can be bidirectional, in the sense that the causal factors can be both biological and environmental. That is, the environment can shape the biology and the biology can affect the environment. In the second place, no mental disorder has specific biological markers identifying it. Third, the weight on inheritability is very relative, as it does not surpass 50% of the variability in any trait or symptom. Finally, the current categories of mental disorders are not associated with an expected response to a treatment. In addition, the study of personality is a paradigmatic example of the complexity of the brain-mind relation: while the mind cannot be understood without the brain, the mental processes have emergent properties that cannot be explained only on the cell level.

Considering these limitations, the epigenetic studies done up to now have mainly been performed in subjects diagnosed of borderline personality disorder (BPD) and they confirm the alterations in DNA methylation processes and histone modification. A recently published work<sup>44</sup> found an association between maltreatment in early childhood and greater BDNF methylation in BPD subjects. Furthermore, the methylation in this gene increased in the patients who did not respond to psychotherapy while the degree of methylation in BDNF decreased in those who improved. This same group observed that the severity of sexual abuse in early childhood correlated with greater methylation of the glucocorticoid receptor in the BPD subjects.<sup>21</sup> These results mean that there is less effect of negative regulation of the glucocorticoid receptor on the HPA function and the HPA hyperfunction has been proposed as an important mechanism that affect the psychopathology of the adult and more specifically can favor the development of BPD.<sup>45</sup> Similar results have been associated sexual abuse in early childhood with greater methylation of the serotonin transporter gene and the degree of methylation of this gene with the symptoms

of antisocial disorder in a community sample of women.<sup>46</sup> Furthermore, the relation between the serotonin transporter methylation and symptoms of antisocial disorder was more intense in the carriers of the "s" allele of the serotonin transporter.

Finally, another work observed greater methylation in 5 genes involved in the development of neuropsychiatric disorders: HTR2A (serotonin receptor), NR3C1 (glucocorticoid receptor), MAOA (monoamine oxidase enzyme), MAOB (monoaminooxidase enzyme), S-COMT (Catechol-O-Methyltransferase enzyme) in a group of BPD patients,<sup>47</sup> with greater methylation in the subgroup of women. These alterations in methylation can decrease the function of the genes involved and thus contribute to the development of BPD. It has also been observed that depression of the mother during pregnancy affects the response to stress of the children in infancy,<sup>48</sup> and it has been proposed that stress in early childhood can epigenetically shape the expression of the genotypes that affect the shaping of the types of attachment with greater risk of developing a BPD.<sup>45</sup>

## CONCLUSIONS

Research on the influence of epigenetic factors in the expression of psychopathology and personality is very encouraging although it is in a preliminary stage. The direction of this knowledge orients us towards the study of the type of experiences capable of modifying the epigenome underlying the psychopathology. Better knowledge of these factors would lead to better detection and avoidance of early pathogenic experiences.<sup>5</sup> Furthermore, epigenetics highlights the biological value of experiences that a subject is exposed to in infancy and those during his/her lifetime, as it indicates that the environment can shape the activation of genes that determine a certain psychopathological phenotype. For example, it has been verified that environmental adversity in infancy activates epigenetic mechanisms that increase the response of the HPA axis to stressant stimuli, a phenotype found in different personality disorders, such as BPD or cluster C disorders (anxious). This knowledge may help the clinicians involved in the treatment of patients with PD to better understand how their patients may have developed the most maladaptive traits, developing hypotheses based on gene-environmental interaction. Similarly, these results may have special importance in the design of prevention programs, that must be enriched with the integration of the genomic perspective, since rearing not only affects behavior and emotion of the child but also the neurohormonal function and the expression of the genotype.<sup>34,49</sup>

On the other hand, epigenetic research has demonstrated that some phenotypic expressions can be altered through epigenetic changes caused by pharmacological treatments. These results are very encouraging although at present they

are too nonspecific. Future studies could be focused on substances that compensate pathological epigenetic patterns. For example, current lines of study propose that decrease of BDNF is directly involved in the pathophysiology of depression and that the restoration of BDNF mediated by antidepressant treatment contributes to the improvement of the depressive state on reversing epigenetic modifications induced by traumatic events and stress.<sup>50</sup>

Investigations indicating the value of the experiences in the modification of epigenetic patterns have also been reviewed. This suggests that psychotherapy, insofar as it promotes the launching of new behaviors and exposure to new environments, may be effective to modify not only behavior and personality but also the expression of the genes underlying behaviors and dysfunctional traits.<sup>51</sup> Specifically, it has been pointed out that therapeutic interventions using environmental enrichment to improve the subjects support network (promoting maternal care, satisfactory family environment, support of nearby friends) have the capacity of attenuating the influence of abuse in infancy on the risk of suffering depression.<sup>29,52</sup> Along these same lines, recent works have found that BPD patients responding to psychotherapy decrease methylation in the BDNF gene.<sup>44</sup> In this study, it is interesting to observe that the psychotherapy used has an intensive character with daily group and individual therapy. Other works that have shown significant clinical improvements accompanied by changes in brain metabolism of glucose in obsessive-compulsive patients also used high-intensity treatment protocols, with daily psychotherapy and daily performance of several hours of exposure tasks with prevention of response.<sup>53</sup> These data seem consistent with some observations<sup>54</sup> that indicate that elevated intensity of the environmental factor is a critical aspect in the production of epigenetic effects.

Finally, the influence of environmental enrichment on the epigenetics of response to stress has been pointed out. It is of interest to observe how the psychotherapeutic programs almost universally incorporate these orientations of treatment in form of recommendations of physical exercise, improved use of free time, frequency of social relationships and participation in recreational activities. As a whole, these findings seem to support the words of the Noble Prize recipient Erik Kandel<sup>55</sup> when he stated that "psychotherapy is effective and produces long term changes in behavior; it presumably does so through learning, by producing changes in the expression of genes that alter the anatomical pattern of interactions between neurons."

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