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Neurogenetics and Epigenetics in Impulsive Behaviour: Impact on Reward Circuitry

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Abstract

Adverse, unfavourable life conditions, particularly during early life stages and infancy, can lead to epigenetic regulation of genes involved in stress-response, behavioral disinhibition, and cognitive-emotional systems. Over time, the ultimate final outcome can be expressed through behaviors bedeviled by problems with impulse control, such as eating disorders, alcoholism, and indiscriminate social behavior. While many reward gene polymorphisms are involved in impulsive behaviors, a polymorphism by itself may not translate to the development of a particular behavioral disorder unless it is impacted by epigenetic effects. Brain-derived neurotrophic factor (BDNF) affects the development and integrity of the noradrenergic, dopaminergic, serotonergic, glutamatergic, and cholinergic neurotransmitter systems, and plasma levels of the neurotrophin are associated with both cognitive and aggressive impulsiveness. Epigenetic mechanisms associated with a multitude of environmental factors, including premature birth, low birth weight, prenatal tobacco exposure, non-intact family, young maternal age at birth of the target child, paternal history of antisocial behavior, and maternal depression, alter the developmental trajectories for several neuropsychiatric disorders. These mechanisms affect brain development and integrity at several levels that determine structure and function in resolving the final behavioral expressions.

Keywords: Epigenetics; Disinhibition; Eating disorder; Alcoholism; BDNF

Introduction

Epigenetics is the study of mitotically and/or meiotically heritable changes in gene function that are not explained by changes in DNA sequence [1]. Epigenetic structural adaptations represent changes in chromosomal regions for registering, signaling, or perpetuating altered activity states [2]. Those heritable changes in genome function, occurring without DNA sequence alteration, involve transference of gene expression patterns not only during the life of a cell, but also over cell generations. The alteration of gene expression is environment-induced, and it occurs during cell differentiation. In other words, non-genetic factors induce the genes to "express themselves" differently [3]. Thus, epigenetics provides a possible interface between the genetic and environmental factors that in combination produce the phenotype. One operational definition of epigenetics [4] involves: (a) an *epigenator*, originating from the environment and triggering the epigenetic pathway, (b) an *epigenetic initiator*, receiving the signal from the epigenator and capable of determining the precise chromatin location and/or DNA environment for the establishment of the epigenetic pathway, and (c) an *epigenetic maintainer*, functioning to sustain the chromatin environment in the initial and succeeding generations. The persistence of the chromatin milieu may require cooperation between the Initiator and the maintainer.

Consideration of the early life programming and transcriptional regulation in adult exposures supports a serious need to understand epigenetic mechanisms as a critical determinant in disease predisposition. It is important, therefore, to combine the latest insights gained from clinical and epidemiological studies with potential epigenetic mechanisms derived from basic research [5]. Moreover, as the significance of epigenetics for neuropsychiatric disorders unfolds with a plethora of descriptive and causal analyses that demonstrate the complexity surrounding etiopathogenesis in each disease state, it becomes increasingly necessary to identify certain consistently emerging aspects of individual liability [6]. Because of limitations inherent in studying human brain samples, many well-designed studies linking epigenetics to behavioral phenotypes employ non human animal models. Also, limitations of brain specimen assays and analyses have led to the nearly exclusive application of peripheral blood samples or buccal swabs. In the former, the epigenome of the different cells with a distinctive DNA methylome is measured, implying that any variation in cell composition, e.g., due to infection, may lead to epigenetic changes that reflect only a shift in cell populations. Much care must be pursued in drawing causal relations between behavioural representations and epigenetics on the basis of peripheral tissues. In other words, one must be cognizant of limitations of studying the epigenome in the context of behavioural attributes, expressions, and outcomes. Ideally, the validation of any such research would incorporate the simultaneous analysis of epigenetic patterns in blood samples and brain structures in a selected animal model under different conditions.

Epigenetics helps to reveal processes through which inherited characteristics and environmental influences shape individual substrates through a variety of mechanisms. These epigenetic mechanisms affect both brain structure and function involved in neurodevelopment, neuronal activity, and neurocognitive processes. Thus, epigenetic regulation affects a multitude of structural entities that determine electrochemical processes in the body: neural differentiation

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[7], astrocytic differentiation [8], oligo dendrocytic differentiation [9], adult neurogenesis [10,11], synaptic plasticity [12,13], and neuro protection against apoptosis [14] and neuronal excitotoxicity [15], and maintenance of neuronal identity [16].

Gräff et al. [17] have reviewed the implications of epigenetic mechanisms that modulate physiological and pathological brain processes. They described the necessity to disentangle regional and cell-type specific epigenetic codes in given environments. During both the prenatal and postnatal periods, for example, an individual's early environment determines the extent of stress resistance that he/she is capable of, thereby constituting the level of stress vulnerability and eventual inappropriate stress coping for that individual [18,19]. In the search for epigenetic mechanisms regulating loss of impulse control by individuals, brain signaling and activity relations in disorders characterized by impulsiveness provide a basis for examination [20].

Genetically mediated variability, currently mapped onto trajectories for psychopathology risk or healthy quality-of-life, whether precipitated by environmental adversity [21] or optimized by health-promoting interventions [22] defines the biological pathways that give rise to phenotypic expressions of individual differences. A variety of exogenous or endogenous perturbations during early development may impact upon epigenetic alterations of gene expression thereby altering the developmental trajectory of an individual's brain. For example, maternal diet may program offspring growth and metabolic pathways thereby instigating a lifelong susceptibility to cognitive or emotional problems and diabetes leading to obesity [23-25]. Moreover, maternal psychosocial experiences [26,27] can induce programming effects on the developing offspring's brain. Environmental factors, primarily during early development, are crucial to the establishment of stable but reversible changes that alter the transcriptional expression and are transgene rationally heritable, with potential concomitant effects on the development of eating disorders and body weight control. Stress during the early-life period, such as physical maltreatment arising from abuse or bullying, induces long-lasting effects on the hypothalamic-pituitary-adrenal axis (HPA) and is associated with blunted HPA reactivity in adulthood as described by evidence from human and nonhuman animal studies [28]; these types of stress are both chronic and acute, and are traumatic.

These adverse childhood experiences are linked to persistent changes in stress-related systems and brain regions involved in mood, cognition, and behavior. For example, Oullet-Morin et al. [29] have observed that bullied and nonbullied discordant monozygotic twins showed distinct patterns of cortisol secretion following a psychological stress test. It was found that bullied twins exhibited a blunted cortisol response compared with their non-bullied discordant monozygotic co-twins, who showed the expected increase. This difference in cortisol response to stress could not be attributed to the children's genetic makeup, their familial environments, pre-existing and concomitant individual factors, or the perception of stress and emotional response to the psychological stress test. The authors interpreted these results as providing evidence for a causal effect of adverse childhood experiences (bullying) on the neuroendocrine response to stress. Nonetheless, to what extent the causal effects of early stressful experiences are responsible for the physiological response to stress in individuals remains to be clarified, since the impact of these experiences awaits the study of interactive genetic and shared environmental influences.

Impulsive behaviors

Impulsiveness is a personal attribute characterized by the individual's tendency to engage in behaviors without adequate forethought as to the consequences of the actions. Impulsive individuals act upon impulses on the spur of the moment rather than after considered thoughts; the behaviors appear motivated by or the result of impulses. Impulsive behaviors may be expressed through positive or negative urgency, the tendency to act rashly while in a positive or in a negative mood. Impulsiveness is associated with instability in cognitive and emotional domains, leading to behavioral problems in several different neuropsychiatric conditions [30]. Cosi et al. [31] have shown that impulsiveness was related to estimations of anxiety, depression, and aggressive behavior in children between 9 and 13 years. They observed higher relationships with measures of internalizing symptoms than with aggression. Motor impulsivity, a component of impulsivity related to inhibition deficits, was the component most related to anxiety and depression. Cognitive impulsivity, on the other hand, was negatively related to anxiety and depression.

The relationships observed between impulsivity and symptoms of internalizing disorders support notions that impulsivity ought to be considered not only in externalizing problems, but also in affective disorders in children and adolescents. Using self-report instruments (Barratt Impulsiveness Scale, BIS; Zimbardo Time Perspective Inventory, ZTPI), Wittmann et al. [32] studied the influence of impulsiveness on brain activation patterns measured by event-related functional magnetic resonance imaging (fMRI) during the encoding and reproduction of intervals with durations of 3, 9 and 18 seconds. The 27 participants included 15 high impulsive subjects according to their self-rating. Brain activations during the duration reproduction task were correlated with measures of impulsiveness. Brain activations during the reproduction phase of the timing task were significantly correlated with reproduced duration, as well as with BIS and ZTPI subscales. These were linked to motor execution as well as to a*core control network* that encompass the inferior frontal and medial frontal cortices, the anterior insula, as well as the inferior parietal cortex. The greater activation in these regions, the shorter was the reproduced intervals, the more impulsive was an individual, and the less pronounced was the future perspective.

As noted earlier, epigenetics describes the study of heritable changes in genome function without DNA sequence alteration. Cellular differentiation provides an example of epigenetic change, and epigenetic regulation of gene expression affects diverse processes such as brain development and differentiation, plasticity, neuron maintenance, and survival. Transgenerational epigenetic inheritance is present in widely differing species [33-35]. Therefore, nonhuman animal laboratory modelshave offered insights that may define and elucidate symptom profiles and causal relationships in epigenetic regulation of gene expression [36,37]. For example, Zhang and Meaney [38], in their review of studies that originated from rodent models, described how environmental signals activate other signals that remodel directly the "epigenome," thereby leading to changes in gene expression and neural function during early and adult life. Weaver [39] described evidence from human and nonhuman animal studies investigating the associations between early life experiences (including parent-infant bonding), HPA activity, brain development, and health outcome. This evidence provides important clues into the neurobiological mechanisms that mediate the contribution of stressful

experiences to personality development and the manifestation of illness.

Adverse fetal and early life conditions are associated with disturbances in normal brain development that may or may not be expressed through disorders evolving primarily from loss of planning ability and impulse control [40]. The developmental origins of health or ill-health involving life-history transitions present placental, nutritional, and endocrine cues for setting long-term biological, mental, and behavioral strategies in response to local ecological or social conditions. Epigenetic responses to environmental changes, exerted during life-history phase transitions, emerge through the window of developmental plasticity, from preconception to early childhood; these influence development, cell- and tissue-specific gene expression, and risk for disorder status at child and adult levels [41].

Adverse fetal and early life conditions that disturb normal brain development are associated with neuropsychiatric disorders, epigenetic consequences emerging to early expression [42,43]. This early life adversity affecting adolescent and adult behaviour reflects the putative epigenetic mechanisms through which early life environmental influences determine life-long susceptibility to chronic disease states [44,45]. Specific expression of a disorder (e.g., psychosis) integrates the relationship between adverse events during childhood and the disease state with epigenetic processes involving stress-regulating functions of the HPA and the neurobehavioral mechanisms through which specific types of childhood trauma may lead to specific types of (psychotic) experiences [46]. It is noteworthy, despite its complexity, the application of treatment drugs that modify the genome (e.g., DNA methyl transferase inhibitors and histone deacetylase inhibitors) for disorder-related deficits emphasises the significance of epigenome targeting [47]. When the action of one gene is modified by the actions of one or several other "modifier" genes, epistasis occurs. Epistatic genes have their phenotype expressed, while hypostatic genes have altered or suppressed phenotypes with the strength and form of epistasis, an important determinant of disorder propensity [48]. Genetic epistasis offers plausible mechanisms for the etiopathogenesis of neurobehavioral attributes, such as neuropathological impulsiveness, that contribute to neuropsychiatric disorders [49,50]. Measurable *endophenotypes*, both as neuropsychiatric concepts and biomarkers, indicate a point on the pathway between gene to disorder, linked to expressed abnormality, that is reflected in clinically unaffected relatives, vulnerability polymorphisms, and the cognitive-emotional domains [51]. Taken together, the relative contributions of endophenotypes and epistasis in the mediation of epigenetic phenomena may prove essential to diagnosis, intervention, and prognosis [52].

Epigenetic implications modulating impulsiveness

Adverse early-life circumstance is associated with disturbances in normal brain development [43], with maternal care influencing HPA stress responses through tissue-specific effects on gene transcription and epigenetic regulation of glucocorticoid receptor expression [53-55]. Early-life social and environmental stressors, such as childhood abuse, neglect, poverty, and poor nutrition, have been associated with the emergence of mental and physical illness (i.e., anxiety, mood disorders, poor impulse control, psychosis, and drug abuse. Increased risk for neuropsychiatric disorders, involving emotional dysregulation, cognitive inadequacy, and vulnerability for impulsiveness are linked to altered HPA stress responses [56,57]. McGowan et al. [58] examined epigenetic differences in a neuron-specific glucocorticoid receptor (NR3C1) promoter between *post mortem* hippocampus taken from suicide victims with or without a history of childhood abuse. The victims who were abused, i.e., through sexual contact, severe physical abuse, or severe neglect (n = 12), were compared with suicide victims without childhood abuse (n = 12), and control subjects (n = 12). Results for the childhood-adversity suicide victims showed reduced levels of glucocorticoid receptor mRNA, reduced mRNA transcripts bearing the glucocorticoid receptor 1_F split variant, and increased cytosine methylation of an NR3C1 promoter. Additionally, patch-methylated NR3C1 promoter constructs that mimicked the methylation state in the childhood-adversity suicide victims' samples expressed reduced NGFI-A transcription factor binding and NGFI-A-inducible gene transcription.

In this regard, the regulation of HPA axis activity and hippocampus-linked cognitive functioning bears reflection: Khalili-Mahani et al. [59] conducted a fMRI study using tasks known to involve the hippocampal formation comparing stress-responders and non-responders. It was found that the former showed significant differences in hippocampal activation already prior to stress, with higher levels of hippocampal activity and cortisol during the cognitive tasks, suggesting states of hippocampal activation prior to stress might reflect states of vigilance or anxiety. Canli et al. [60], investigating neural correlates of epigenesis, indicated that early-life stress interacts with the effect of serotonin transporter genotype on amygdala and hippocampus resting activation, thereby modulating stress and affective states (see also [61]). Quirin et al. [62] have indicated that the HPA system and hippocampus are programmed during critical development periods, establishing a certain trajectory of physiological responsiveness throughout life. Finally, Lahiri et al. [63] have proposed a "latent early-life associated regulation" (LEARn) model that assigns the latent changes in expression of specific genes. The model posits that epigenetic perturbations primed initially through disturbing environmental events during early-life development, at long-term regulation, produce a neuropathology only later in the life cycle. Thus, genetic and environmental risk factors contribute to the etiopathogenesis of brain disorders all of which express symptoms that, to greater or lesser extent, are affected by dysregulation in the control of impulsive behaviors [64].

Impulsiveness and gene polymorphisms

The notion of impulsiveness incorporates a multidimensional construct consisting of a range of inter-related factors that include novelty-seeking and reckless behavior, lack of planning ability and self-control, with or without aggressiveness, that have associations with various psychopathologies [64-66]. Regression analyses based upon several self-report questionnaire studies including a range of cognitive-emotional personal attributes have indicated that impulsiveness is predicted by negative effect, a motivation, and depressiveness, and counter predicted by positive affect and internal locus of control, in healthy volunteers comprised of adult working populations, students, and adolescents [30,67,68]. It appears that the inability to plan future decisions and subsequent actions presents a critical component of impulsiveness expressed in male offenders classified as both non-psychopathic and psychopathic [69], euthymic and depressed bipolar patients, depressed unipolar patients, and healthy controls [70], as well as in male forensic psychiatric in-patients facing severe criminal charges [65]. Individuals whose behavior is determined by high levels of impulsiveness show impairments over a wide range of neurocognitive tasks including tests of executive functioning [71-73], cognitive tasks demanding response control [74,75], and cognitive flexibility (verbal fluency) [76]. An individual's control of choice and decision-making

processes seems to be modulated largely by the eventual consequences of affective and cognitive appraisals with reinforcement or avoidance of actions directed by the underlying neural circuits [77-80]. Functional gene variants have putative influence on the neural mechanisms of disorders relating to impulsive control, such as functional variants in the serotonin transporter gene 5-HTTlPR [81,82].

Serotonergic systems are involved in neuropsychiatric disorders [83] and regulate the functional domains of cognition and emotion [84]. Both impulsiveness and aggressiveness are associated with serotonergic system functioning [85,86], which may be viewed as traits with complex genetic architecture that is complicated further by epistasis [87], epigenesis [88,89], gender moderation, and ethnicity [90]. In order to investigate the association between the C(-1019)G functional polymorphism, regulating the HTR_{1A} gene expression, and impulsiveness, Benko et al. [91] applied the Impulsiveness subscale (IVE-I) of the Eysenck Impulsiveness, Venturesomeness and Empathy Scale and the Barratt Impulsiveness scale (BIS-11) to a Hungarian population sample of healthy community-based volunteers (n = 725, 596 females). The C (-1019) G genotype groups, GG *versus* GC *versus* CC, showed significant differences: GG type subjects showed significantly higher impulsiveness on the IVE-I scale, for motor and cognitive impulsiveness, and for the total impulsiveness score on the BIS-11 scale. The authors suggested that the receptor gene, HTR_{1A}, expression was involved in a continuum phenotype of impulsiveness.

Other studies have demonstrated links between serotonergic gene polymorphisms, health-hazard behaviours, and impulsiveness [92]. In a predominantly Caucasian (95%) student population (n = 200, 62% female), Stoltenberg and Nag [93] used a mathematical model of genetic control of presynaptic serotonergic function and genotyping of the TPH2 intron-8 (rs1386483) polymorphism and the MAOA u-VNTR amplification to show that simulated levels of CSF-5HIAA levels were correlated negatively with BIS-11 total scores. Pathological gambling, risky-choice behaviour, and faulty decision-making due to impulsiveness were all associated with alterations in serotonergic functioning [94-97], and alterations to 5-HT transporter 5HTTLPR polymorphism [98,99]. Juhasz et al. [100] found that only the TPH2 haplotype of the TPH2, TPH1, SLC6A4, and HTR1A serotonergic gene polymorphisms was linked to risk behaviour assessed with a probabilistic gambling task in a population cohort of 1035 individuals. They observed that carriers of the more prevalent TPH2 displayed lower risk-taking on the cognitive tasks involved with no links between the functional polymorphisms in the TPH1, SLC6A4, and HTR1A genes and risk behaviour. Despite the marked in-roads to gene marking in both patient and healthy volunteer subjects, the genetic links between impulsiveness, whichever the means to assess this behaviour, and the serotonergic pathways suggest the implication, rather than the conclusive involvement, in the condition.

Impulsiveness, aggressiveness, and problems concerning behavioural inhibition, e.g., substance abuse, seem, according to the emerging scenario, inherent to several disorders, including attention deficit hyperactive disorder (ADHD) and borderline personality disorder, that involve impaired neuropsychological functioning and emotional dysregulation [101] and fit the concept known as *Reward Deficiency Syndrome* [102-104]. Reif et al. [105,106] have shown that a polymorphic promoter dinucleotide repeat length variation of the NOS1 gene (NOS1 Ex1f-VNTR) may hold functional significance, with associations of the polymorphism to clinical traits of impulsiveness [106]. Retz et al. [107] have examined the association between self-reported impulsiveness, venturesomeness, and empathy in 182 adult male (young-middle aged), Caucasian offenders referred to forensic psychiatric medicine. The authors assumed that impulsiveness and ventures omeness presented closely related negative facets, while empathy involved positive facets of moral reasoning, prosocial behaviour, and control of aggression [108,109]. They observed that impulsiveness was associated significantly with NOS1 Ex1f-VNTR and violent behaviour, as well as childhood ADHD symptoms, whereas venturesomeness showed only a strong tendency to the same. Empathy was associated significantly with NOS1 Ex1f-VNTR but not violent behavior or childhood ADHD symptoms. Jacob et al. [110] studied the interactions of serotonergic candidate genes (5-HTT, HTR1A, and TPH2) with burden of life events in 183 patients with personality disorders and 123 patients with adult ADHD. They found that only the G allele of HTR1A rs6295 increased risk for erratic emotional-dramatic Cluster B personality disorders, but increased the risk for the anxious-fearful Cluster C personality disorders, thereby indicating that gene effect was modified by stressful life events, or *vice versa*.

ADHD is discussed often on the basis of neurodevelopmentally-inappropriate attentional problems, motor hyperactivity, and impulsiveness that emerge in early-life with disruptions of social and academic functioning. ADHD presents a disorder characterized by marked levels of impulsiveness [111,112], that persists over the individual's lifespan [113-115]. The relevance of epigenetic mechanisms for ADHD etiopathogenesis has been discussed [20,116]; chromosome organization, DNA methylation and transcriptional factors all contribute to the pathophysiology of the disorder [117]. Environmental risk factors for high trajectories of impulsivity-hyperactivity and inattention symptoms were premature birth, low birth weight, prenatal tobacco exposure, non-intact family, young maternal age at birth of the target child, paternal history of antisocial behavior, and maternal depression [118] all of which are clear-cut examples of environmental adverse conditions. Maternal-infant relationships and the social rearing context exert exceedingly profound effects on laboratory animals' emotional reactivity, responses to stress and central levels of BDNF [119]. Whereas reductions/deficits in BDNF are associated invariably with neuropsychiatric disorder conditions [6,120], Chan et al. [22] have observed that advantageous environmental conditions, including fruit intake (higher levels), exercise (higher levels), and television-watching frequency were associated with serum BDNF concentrations in 85 healthy individuals.

Despite much evidence implicating the interactions of serotonergic candidate genes, not all the results available follow the general trends with regard to diagnosed conditions (e.g., ADHD) with impulsiveness as a major symptom. For example, genotype-tagged all common variants within TPH1 and TPH2 genes in a Norwegian sample of 451 adult ADHD patients and 584 healthy controls, together with a meta-analytic sample of 1,636 ADHD cases and 1,923 controls, but failed to obtain consistent evidence of a substantial effect of common genetic variants on persistent ADHD. Using hierarchical linear regression analysis on a sample of 404 youths, Nikolas et al. [121] obtained significant 5HTTLPR x Self-Blame interactions for ADHD symptoms, concluding that both high and low serotonergic activity were risk factors for ADHD when linked with psychosocial distress in relation to inter-parental conflict. Perinatal stress or infection, and/or maternal affective disorder that influence attachment are implicated in the epigenetic mechanisms expressed in long-lasting changes to the HPA axis [122]. Emotional dysregulation, expressed in ADHD and trait-related disruptive disorders as a central aspect [123], progresses

through epigenesis from temperamental difficulties in infancy to problems of impulse control in childhood to substance use debut, with comorbid aggressive-impulsivity [124] in adolescence and eventually severe substance abuse and criminality in young adulthood [125,126].

Disinhibition involves the lack of restraint manifested through several expressions of maladaptive behaviors, including disregard for social conventions, impulsiveness, and poor risk assessment. It affects motor, instinctual, emotional, cognitive, and perceptual aspects with signs and symptoms similar to the diagnostic criteria for manic bouts. Hypersexuality, hyperphagia, and aggressive outbursts are indicative of disinhibited instinctual drives. Disinhibited individuals demonstrate reduced capacity to modulate their immediate impulsive responses to given situations. Flory et al. [127] have presented evidence of an association between functional variation in the prodynorphin (PDYN) gene and a dimensional measure of disinhibited behavior. A 68bp sequence in the core promoter region of the PDYN gene was genotyped in a community sample of 1021 adults aged 30-54. Participants were interviewed for lifetime history of DSM-IV alcohol dependence and completed two self-report measures of sensation seeking and impulsiveness. Fifteen percent (n=151) of the sample met DSM-IV criteria for alcohol dependence, and while results did not support an association between the PDYN polymorphism and the diagnosis of alcohol dependence, they did show an association between the low expressing L allele of the PDYN gene and a preference for engaging in disinhibited behavior. Additionally, people who had both a history of alcohol dependence and higher scores on this Disinhibited Behavior scale were most likely to carry an L allele. These results indicated that variation in the PDYN gene is associated with a dimensional trait or intermediate phenotype that reflects a preference for heavy drinking and engaging in related risky behaviors (e.g., drug use, sexual activity). This work is in agreement with earlier work showing the important relationship between opioid peptides and alcoholism [128] and alcohol preference in genetically bred rodents [129].

Gaming

Behavioral addictions, especially pathological gambling and Internet addiction, have become a growing concern in research and for formulating health policy. Pathological gambling is an impulse control disorder with a suggestive genetic vulnerability component. Pathological gambling has been termed both the *pure* and the *hidden* addiction: Pure because it is not associated with the intake of any addicting substance, and hidden because it is an extension of a common, socially accepted behavior. It has been established in the United States that the estimate of the proportion of variation in liability for a gambling disorder due to genetic influences was 49.2%. Moreover, there has been no evidence for shared environmental influences contributing to variation in liability for a gambling disorder, nor for quantitative or qualitative gender differences in the causes of variation in such liability [130,131]. Among the German population, the estimated prevalence of pathological gambling is 0.2-0.5%, and these numbers are comparable to prevalence rates reported for illegal drug dependency. Thus, about 1.5 million people, i.e., 3% of the German population, are believed to be at risk of Internet addiction [132].

Comings et al. [133] were the first to report highly significant results that related pathological gambling to variants of the dopamine D2 receptor gene. Moreover, there are similarities between behavioral addictions and substance dependency. The Taq A1 variant of the human DRD2 gene has been associated with drug addiction, some forms of severe alcoholism, and other impulsive, addictive behaviors. According to Comings et al. [133], of a sample of 171 pathological gamblers, 50.9% carried the D2A1 allele versus 25.9% of 714 known non-Hispanic Caucasian controls screened to exclude drug and alcohol abuse. For the 102 gamblers who filled out the questionnaires, 63.8% of those in the upper half of the Pathological Gambling Score (more severe) carried the D2A1 allele, compared to 40.9% in the lower half (less severe). Of those who had no co morbid substance abuse, 44.1% carried the D2A1 allele, compared to 60.5% of those who had co morbid substance abuse. Forty-eight controls and 102 gamblers completed a shorter version of the Pathological Gambling Score. Of the 45 controls with a score of zero, 17.8% carried the D2A1 allele. Of the 99 gamblers with a score of 5 or more, 52.5% carried the D2A1 allele. The authors suggested that genetic variants at the DRD2 gene play a role in pathological gambling, and support the concept that variants of this gene are a risk factor for impulsive and addictive behaviors. This work has been consistently confirmed by others and most recently by Lobo et al. [134] who evaluated the association of genetic variants in the dopaminergic receptor genes (DRD1-3s) with risk for gambling in healthy subjects using the Canadian Problem Gambling Index (CPGI). Healthy Caucasian subjects who had gambled at least once in their lifetime (n=242) were included in the analysis. Gender was not associated with the CPGI, while younger age was associated with higher CPGI scores. They have found that none of the single polymorphisms investigated on DRD1 and DRD3 were associated with CPGI scores in healthy subjects. However, in support of Comings earlier work, they observed trends for association on the TaqIA/rs1800497 polymorphism and the haplotype flanking DRD2 (G/C/A), thereby providing further evidence for the role of dopamine D2-like receptors in addiction susceptibility.

Additional research has supported the view that Internet addiction is associated with abnormalities in the dopaminergic brain system. [135] using PET imaging showed reduced levels of dopamine D2 receptor availability in subdivisions of the striatum including the bilateral dorsal caudate and right putamen, in subjects with Internet addiction. Results from our laboratory have suggested that dopamine agonist therapy instead of dopamine blockade seems more parsimonious [136]. Moreover, Han et al. [137] reported that the weak inhibitor of dopamine — a nor epinephrine reuptake Bupropion sustained release — after a six week period induced a decrease in craving for Internet video game play, total game play time, and cue-induced brain activity in dorsolateral prefrontal cortex. This effect is similar to similar to other addictions due to reward circuitry impairments.

In one study by Lee et al. [138], a group of excessive Internet users had higher SS-5HTTLPR frequencies, harm avoidance, and Beck Depression Inventory scores than control subjects. SS-5HTTLPR expression was closely related to harm avoidance in the excessive Internet users. The results of this study suggested that excessive Internet users may have genetic and personality traits similar to depressed patients.

Aggression

Human aggression and impulsivity-related traits have a complex background that is greatly influenced by genetic and non-genetic factors [139]. It is well known that the dysfunction of neural circuits responsible for emotional control represents a causal factor of violent behaviors. Dysfunctional brain areas responsible for violent antisocial behavior and psychopathology include the frontal and temporal lobes, especially orbital and medial frontal regions (anterior cingulate cortex) and the amygdala [140]. Excessive reactivity in the amygdala coupled with inadequate prefrontal regulation serves to

increase the likelihood of aggressive behavior in both adolescents and adults. Developmental alterations in prefrontal-subcortical circuitry as well as neuromodulatory and hormonal abnormalities play a role. Accordingly, it has been exposed that imbalance in testosterone/serotonin and testosterone/cortisol ratios (e.g., increased testosterone levels and reduced cortisol levels) increases the propensity toward aggression because of reduced activation of the neural circuitry of impulse control and self-regulation.

The main biological systems that are known to be involved are certain reward neurotransmitters including: serotonin, opioid peptides, gamma-aminobutyric acid, and the catecholamines (dopamine and norepinephrine), which can become disturbed through epigenetic influences. Chen at al. [141] hypothesized that pathological aggression, a complex behavioral disorder, in adolescents may in part involve polymorphisms of the dopaminergic system. While a number of neurotransmitter systems must be involved, due to polygenic inheritance, there is increasing evidence that one major pathway deserving special consideration is the dopaminergic system. Importantly, however, advances in our knowledge of the neurobiology of aggression and violence have given rise to rational pharmacological treatments for these behaviors.

It is our notion that pathological aggressive behavior has, at least in part, similar underlying biological underpinnings to other forms of impulsive behaviors such as pathological gambling. By analogy to drug dependence, it has been speculated that the underlying pathology in pathological gambling is a reduction in the sensitivity of the reward system. While studying pathological gamblers and controls during a guessing game using fMRI, Reuter et al. [142] observed a reduction of ventral striatal and ventromedial prefrontal activation in the pathological gamblers that were negatively correlated with gambling severity. Subsequently, linking hypo activation of these areas to disease severity. A positive correlation of both the DRD2 gene and the dopamine transporter gene (DAT1) polymorphisms were observed with pathological violence in adolescents in a blinded clinical trial. Thus, this and other cited works suggest a role both for the DRD2 and the DAT genes in pathological aggressive behavior. Chen et al. [141] hypothesized that pathological aggression, a complex behavioral disorder, in adolescents may in part involve polymorphisms of the dopaminergic system. Hefurther hypothesized that follow-up gene research in this area, albeit premature, resulting in confirmation of positive correlations with dopaminergic polymorphisms, and utilizing highly screened controls (eliminating any addictive, compulsive, and impulsive behaviors in both proband and family) may have important ramifications in our young population. This concept has been confirmed by additional work by Vaske et al. [143] showing that offenders, on average, are more likely to be violently victimized than non offenders. Their study used data from the National Longitudinal Study of Adolescent Health to investigate whether variants of a polymorphism in the dopamine D2 receptor gene (DRD2) distinguish between offenders who are violently victimized and offenders who are not violently victimized. The results showed that offenders who are violently victimized are more likely to carry the DRD2 (A1) risk allele than offenders who have not been violently victimized.

Furthermore, Retz et al. [144] reported an association of the dopamine D3 receptor (DRD3) polymorphism with impulsiveness. This association was detected in a group of violent offenders, but not in non-violent individuals. Highest scores on several impulsiveness scales were found in heterozygous violent individuals, while homozygotes showed significantly lower rating scores, suggesting a heterosis effect. The results of their study suggest that variations of the DRD3 gene are likely involved in the regulation of impulsivity and some psychopathological aspects of violent behavior.

Based on the work of Pavlov et al. [145] serotonin facilitates prefrontal inhibition, and thus insufficient serotonergic activity can enhance aggression. According to Pavlov et al. [145], genetic predisposition to aggression appears to be deeply affected by the polymorphic genetic variants of the serotoninergic system that influences serotonin levels in the central and peripheral nervous systems, as well as the biological effects of this hormone, including rate of serotonin production, synaptic release, and degradation. Among these variants, functional polymorphisms in the monoamine oxidase A (MAOA) and serotonin transporter (5-HTT) may be of particular importance due to the relationship between these polymorphic variants and anatomical changes in the limbic system of aggressive people. Furthermore, functional variants of MAOA and 5-HTT are capable of mediating the influence of environmental factors on aggression-related traits. Other reports in the literature consistently support the role of reward genes in suicidal, aggressive, and violent behaviors [146-148].

Epigenetics of impulsiveness in eating disorders

Problems arising with impulse control often can be expressed in the form of behavioral extremes, such as with excessive eating behavior [149]. Individuals presenting eating disorders also may show an impulse control disorder with co-morbid obsessive-compulsive disorder [150]. It has been observed that individuals with bulimia nervosaplus lifetime impulse control disorder/self-injurious behavior presented more extreme personality profiles, especially on novelty seeking and impulsivity, and general psychopathology, or more affective, interpersonal and impulse-control problems linked to temperamental traits, than individuals with bulimia nervosa/eating disorder without impulse control disorder/self-injurious behavior [151,152]. Behavior excessiveness associated with impulse control problems have been observed also in Parkinson's disease patients [153,154]. Eating disorders share neuropsychiatric co-morbidity and certain susceptibility genes with mood disorder, impulsiveness and substance abuse [155,156] with greater suicide prevalence among anorexia nervosa patients [157]. Tchanturia et al. [158] have found impaired decision-making in both male and female patients presenting eating disorder. Concurrently, it was shown that internalizing problems (cf. anxiety, depression and somatization) preceded the development of anorexia nervosa, whereas both internalizing and externalizing behavior problems (aggressive and delinquent behavior) preceded bulimic disorders [159]. Van Camp et al. [160] have obtained a significant association of WNT10B, in the Wnt pathway, with body mass index (BMI) for three of their genotyped tagSNPs (rs4018511, rs10875902, rs833841) in a case-control population of Belgian men as analyzed by logistic regression. Allelic heterogeneity testing demonstrated that these associations all represent the same significant signal. They observed also that two of the three significant SNPs were linked with BMI and weight in the male population (linear regression analysis). The authors concluded that common variation in WNT10B was shown to be associated with BMI and weight.

Epigenetic investigations of eating disorders have shown significant global DNA hypomethylation in lymphocytes of anorexia nervosa patients, with decreased expression of α-synuclein gene linked to α-synuclein gene promoter [161]. Frieling et al. [162] also observed lower levels over atrial natriuretic peptide mRNA accompanied by

hyper methylation of the atrial natriuretic peptide gene (in the bulimia nervosa subgroup) in patients presenting eating disorders. A disturbed expression of dopaminergic genes is accompanied by a dysregulation of the epigenetic DNA methylation in eating disorder. Individuals presenting eating disorders were found to display epigenetic changes in dopaminergic genes [163]; here, patients showed an elevated expression of DAT mRNA when compared with the controls and a down-regulation of the DRD2 expression. The up regulation of the DAT gene was accompanied by a hyper methylation of the gene's promoter in the anorexia nervosa and bulimia nervosa group, while a significant hyper methylation of the DRD2 promoter was only present in the anorexia nervosa group [164]. It appears that the pattern of proopio melanocortin regulation implicates the epigenetic association with the underweight state rather than with persisting trait markers of anorexia nervosa, thereby precluding its role in impulsive behavior. Campbell et al. [165] have indicated that diverse adaptability in the systems regulating energy homeostasis with regard to population and individual differences may contribute to lifetime risk for eating disorders for individuals encumbered by general psychiatric predisposition (impulsive behavior). Thus, risk of development of eating disorders may increase through the epigenetic forces of poor nutrition, obesogenic environment of infancy, and acute or chronic stressors or trauma [166].

Nonhuman animal experiments [135,167,168], as well as human studies [169-171], have indicated that BDNF levels are affected by conditions that are described by disruptions in the control of impulses. Concomitantly, impairments in executive functioning and absence of motivation are associated with abnormalities in brain circuitry involving the prefrontal cortex. Damage within this circuitry often is accompanied by a wide range of expressions of impulsiveness and risky behaviours [172-174]. For example, Ledgerwood et al. [175] compared pathological gamblers and healthy control subjects on several measures of executive functioning (including measures of response inhibition, working memory, cognitive flexibility and perseveration, planning and decision-making) as well as on memory and intelligence tests. Pathological gamblers showed specific deficits on measures of planning and decision-making, and relative deficits on a measure of perseveration compared to controls. Their results imply that pathological gamblers may experience deficits on specific components of executive function. In this regard, patients presenting anorexia nervosa have been found not to perform well in set-shifting tasks (an executive function). Nakazato et al. [176] showed that an anorexia nervosa group made significantly more errors total and perseverative errorson a task sensitive to frontal brain damage, compared to the healthy control group; serum BDNF concentrations were significantly lower in the anorexia nervosa group compared to the healthy control group, and also compared to the anorexia nervosa recovered group. Additionally, an anorexia nervosa group showed significantly impaired ability to shift cognitive sets on the same test, with, concurrently, serum glutamine concentrations in the anorexia nervosa group significantly higher (by approximately 20%) than those in the healthy control group [177].

It is well known that the endocannabinoid system is involved in the regulation of appetite, food intake and energy balance. Central neurochemical systems including the monoamine, opioid, and cannabinoid systems have been promising targets for anti-obesity drugs that modify behavioral components of obesity. In addition to modulating eating behavior, centrally acting anti-obesity drugs also are likely to alter emotional behavior and cognitive function due to the high expression of receptors for the neurochemical systems targeted by these drugs within the fronto-striatal and limbic circuitry and blockade of dopaminergic activity. Drugs targeting the cannabinoid system (rimonabant and taranabant) were consistently associated with symptoms of anxiety and depression, including reports of suicidal ideation. Similar adverse events also have been noted for the D_1/D_5 antagonist ecopipam [178]. Nevertheless it is important to continue to understand the relationship between the endocannabinoid system and eating disorders. Frieling et al. [163] found significantly higher levels of CB(1) receptor mRNA in the blood of patients with anorexia nervosa (AN) and bulimia nervosa (BN) when compared to controls. No differences were found regarding the expression of CB (2) receptor mRNA. Higher CB (1) receptor expression was associated with lower scores in several eating disorder inventory-2 (EDI-2) subscales including perfectionism, impulse regulation, and drive for thinness. Additional points of view concerning reward circuitry and eating disorder recovery have been postulated using neuroimaging tools [179,180].

Epigenetics of impulsiveness in alcohol abuse

Drug addiction, and alcohol addiction in particular, involves a number of aspects that include strongly ingrained compulsive behaviors, a high level of heritability, co-morbidity with other psychiatric conditions, high frequencies for relapse, powerful resistance to treatment therapy that requires high levels of motivation and broad strategies, rareness of condition-insight, and a very long-lasting nature [181]. Thus, addiction may be viewed as a chronic condition of compulsive drug seeking and use that is mediated by stable changes in central reward pathways [182,183], whereby the transient and potentially stable conditions underlying epigenetic mechanisms result inmolecular mechanisms impacting upon neuronal changes that give arise to prolonged behavioral changes [184]. Drug-abusing individuals who display high delay discounting rates (preference for a reward that arrives sooner rather than later) express higher impulsiveness scores in comparison with healthy controls, as evidenced with addicts undergoing methadone treatment [185]. Fontenelle et al. [186] have argued that obsessive-compulsive disorder, impulse control disorders and substance-related disorders overlap on different levels, including phenomenology, co-morbidity, neurocircuitry, neurocognition, neurochemistry and family history. Impaired executive and prefrontal cortex functioning are invariably associated with addictive behaviors and poor impulse control [187-189]. Prolonged use of addictive drugs alters gene expression in brain reward centers by promoting alterations in histone acetylation, phosphorylation, methylation, and DNA methylation levels in the nucleus accumbens (NAc) [190-192]. Many changes in gene transcription under conditions of prolonged substance abuse are coordinated by a complex series of histone modifications surrounding DNA that result in either repression or activation of gene expression [193]. The genetic basis, mechanisms of action and gene-environment interactions in alcoholism remain unknown to great extent [194]. Nevertheless, lifestyle factors including nutrition, daily behaviors, stress, physical activity, working hours, smoking and alcohol consumption influence and modify epigenetic mechanisms [195-197]. Given the fact that alcohol-dependence seems highly heritable (50 to 60% of the variance in men and women alike), polymorphisms of genes influencing alcohol metabolism, GABAergic, dopaminergic and serotonergic neurotransmission seem, indeed, at stake in the development of alcohol-dependence and its related features such as personality and behavior, including impulse control or craving [198].

There are numerous putative causal link between prenatal

vulnerability of future parental epigenomes damaging environmental factors aggravated by abnormal socio-cultural conditions (including, for instance, malnutrition and chronic stress) and the alarming risk of developing heritable complex neuropsychiatric conditions later in life [199-201]. Primordial germ cells, embryos, and fetuses are highly susceptible to epigenetic dysregulation by environmental agents, such as drugs, which may through different mechanisms, exert multiple adverse effects [202]. For instance, DiNieri et al. [203] studied the striatal dopamine and opioid-related genes in human fetal subjects exposed prenatally to cannabis (as well as cigarettes and alcohol). This cannabis exposure during the prenatal period decreased DRD2 messenger RNA expression in the human ventral striatum (including the NAc). They observed that cigarette use by the mothers was associated with reduced NAcprodynorphin messenger RNA expression, and alcohol exposure induced broad alterations primarily in the dorsal striatum of most genes. Pregnant rats were exposed to Δ-9-tetrahydrocannabinol (THC) and the epigenetic regulation of the NAc DRD2 gene in their offspring at postnatal Day 2, comparable to the human fetal period studied, and were examined in adulthood [203]. It was found that chromatin immune precipitation of the adult NAc revealed increased 2meH3K9 repressive mark and decreased 3meH3K4 and RNA polymerase II at the DRD2 gene locus in the THC-exposed offspring. Decreased DRD2 expression was accompanied by reduced dopamine D2 receptor (D (2) R) binding sites and increased sensitivity to opiate reward in adulthood. They concluded that maternal cannabis use altered developmental regulation of mesolimbic D (2) R in offspring through epigenetic mechanisms that regulate histone lysine methylation, and the ensuing reduction of D (2) R might contribute to addiction vulnerability later in life. In addition, there appeared to be a direct role for chromatin remodeling in the regulation and stability of drug-mediated neuronal gene programs and the subsequent promulgation of addictive behaviors [191].

Alcoholism involves compulsive and uncontrolled consumption of alcoholic beverages, generally detrimental to the individual drinker's health, personal relationships, occupation and social standing. The disorder often involves affective symptoms, such as in depression, and high levels of impulsiveness [204], and in alcohol-dependent patients a strong relationship exists between depressiveness and impulsiveness [205]. It has been shown that high levels of impulsiveness/impulse control problems seem to elevate vulnerability for development of alcohol dependence, as well as being predictive for poor outcome measures. Jakubczyk et al. [206] have presented results indicating a significant association between high levels of behavioral impulsivity and the C/C genotype, linked to reductions in 5HT2A receptors in the CNS, of rs6313 in a group of 304 alcohol-dependent patients. Other important reports concerning reward gene polymorphisms and alcoholism add to the large scientific knowledge of gene-by-environment implications for both prevention and treatment targets [194, 207-209].

Epigenetic regulation of BDNF in impulse control disorders

Both cognitive and emotional impulsivity have been associated with plasma levels of BDNF [210], and BDNF single nucleotide polymorphisms [211,212]. The neurotrophin affects the development and integrity of the noradrenergic, dopaminergic serotonergic, glutamatergic and cholinergic neurotransmitter systems [213-215]. Additionally, BDNF has been found to exert important influences upon feeding behavior, food intake regulation, energy metabolism and weight control in young and adult individuals [216-218]. Links have been established between various forms of impulse control disorders or psychopathological traits with alterations of BDNF integrity [219-221]. A common polymorphism of the human BDNF gene, Val^{66}Met that affects human memory-related hippocampal activity and performance [222], has been associated with different forms of eating disorders, alterations in BMI values and obesity in adult populations [223-225]. Skledar et al. [226] have demonstrated a significant association between the presence of one or two Met alleles and obesity in ethnically homogenous groups of healthy Caucasian children and adolescents. Timpano et al. [227] studied the BDNF gene in a large (N=301) clinical sample of patients presenting obsessive-compulsive disorder, who were classified as hoarding or non-hoarding types. Compulsive hoarding (pathological collecting) presents a behavioral pattern characterized by excessive acquisitiveness and inability/unwillingness to discard large quantities of objects that would seemingly qualify as useless or without value. Compulsive hoarding behavior is linked to health risks, impaired functioning, economic burden, and adverse effects on caregivers. It was observed that the Val/Val genotype was linked with the hoarding type and more severe hoarding behaviors, as well as greater BMI levels. Hoarding levels also were associated with greater BMI scores; hoarding individuals were much more likely to be classified as obese compared with the non-hoarding type. There appears to be a complex gene, body weight, and psychopathology interaction whereby a primitive, survival "thrifty gene" strategy may be conserved and represented in a subgroup of individuals manifesting severe hoarding symptoms.

Extreme early care giving adversity—a possible consequence of certain types of institutionalized up-bringing—may be associated with a range of negative behavioral and psychological outcomes [228] and a variety of persistent clinical and behavioral disorders [229]. In a group of institutionalized Romanian children adopted into UK families, it was observed that the pattern of normality/impairment was mainly established by 6 years of age, with considerable continuity at the individual level between 6 and 11 years [230,231]. Indiscriminate social behavior has been observed across studies of children reared in institutions and a part of a deprivation-specific pattern [232]. The major features of indiscriminate social behavior include: lack of reticence with unfamiliar adults, inappropriate social boundaries and affection with strangers and failure to check back with a familiar caregiver when in an unfamiliar setting. Likewise, the BDNF gene is associated with a wide range of neuropsychiatric conditions comorbid with problems of impulse control [233-236]. Drury et al. [237] compared a group of abandoned Romanian children (between 6 and 30 months of age) assigned to a "care-as-usual" (CAUG, n = 68) or a foster care (FCG, n = 68) condition after exclusion criteria, genetic syndromes, fetal alcohol syndrome and microcephaly, were met. Indiscriminate social behavior was assessed at four time points: Baseline, 30, 42 and 54 months-of-age. It was observed that children with either the s/s 5httlpr genotype or met66 carriers in BDNF presented the lowest levels of indiscriminate social behavior in the FCG condition and the highest levels in the CAUG. Children randomized to institutional CAUG with both plasticity genotypes presented the most signs of indiscriminate social behavior whereas those with both plasticity genotypes assigned to the FCG condition presented the fewest signs at 54 months. Children with no plasticity alleles showed no intervention effect upon indiscriminate social behavior at 54 months. These findings provided further evidence of gene-by-environment interaction in the context of differential susceptibility to institutionalized, adverse care environments [238, 239].

Limitations

One limitation of many of the studies reviewed here pertains to the small DNA methylation differences considered relevant when significant levels are observed. It seems to be the case that biologically-relevant differences, linked to the sensitivity of the epigenetic techniques that often failed to exceed 10%, ought to accompany the statistically significant differences. DNA methylation in pure cell populations follows a trimodal distribution: un methylated; partially methylated (e.g., imprinted genes); and methylated. Generally, minor differences in DNA methylation may exert no impact on gene expression while for most genes clear-cut changes are necessary for differences to appear, e.g., from unmethylated to partially methylated or completely methylated. Despite the limitation that has provided doubts concerning a number of studies, one ought not to be blinded to promising avenues: Nonhuman animal models designed to investigate fetal alcohol spectrum disorders, intimately involved in impulsive behaviors and reward circuitry,can serve to(i) identify genetic and epigenetic modifications that may be predictive of the neurobehavioral and neurobiological dysfunctions in offspring induced by gestational alcohol exposure, and (ii) determine the relationship between structural alterations in the brain induced by gestational alcohol exposure and functional outcomes in offspring [240]. Prevailing notions from a variety of studies support the contention that neurobehavioral and neurobiological dysfunctions induced by gestational alcohol exposure are correlated with the genetic background of the affected offspring and/or epigenetic modifications in gene expression.

Conclusions

The results of human and nonhuman animal studies have suggested that early-life adversity can lead to epigenetic regulation of genes involved in stress-response, behavioral disinhibition and cognitive-emotional systems. Turecki et al. [241] have described how early-life adversity increases risk of suicide in susceptible individuals by disrupting the development of stable emotional, behavioral and cognitive phenotypes that are likely to result from the epigenetic regulation of the hypothalamic-pituitary-adrenal axis and other systems involved in responses to chronic or acute traumatic stress. The diversity of interactions between genetic and epigenetic factors that may or may not confer flexibility on the epigenome is expressed in adaptability. Taken together, there are several avenues implicating epigenetic processes underlying the final outcome of pathological impulsiveness in neuropsychiatric disorders that associate not only serotonergic and dopaminergic [242] systems but also MAO-activity and COMT [243] genes, and even the neuropeptide Y gene [244] in the disease etiopathogenesis. In all likelihood, greater complexity of epigenetic mechanisms awaits both description and assimilation into prevailing notions. Finally, early life events may have important effects on gene expression and as such must be evaluated in patient history questionnaires [39]. In fact recent evidence from rodent studies suggests that maternal care in the first week of postnatal life establishes diverse and stable phenotypes in the offspring through epigenetic modification of genes expressed in the brain that shape neuroendocrine and behavioral stress responsivity throughout life.

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