This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author(s) and source are credited.



ISSN:2157-7412

Journal of Genetic Syndromes & Gene Therapy

The International Open Access Journal of Genetic Syndromes & Gene Therapy

Executive Editors

Kenneth Blum University Of Florida, USA

Lee Philip Shulman Northwestern University, Chicago

Jasti S.Rao University of Illinois College of Medicine, USA

Roland W. Herzog University of Florida, USA

Gregory M. Pastores New York University School of Medicine, New York

Available online at: OMICS Publishing Group (www.omicsonline.org)

This article was originally published in a journal by OMICS Publishing Group, and the attached copy is provided by OMICS Publishing Group for the author's benefit and for the benefit of the author's institution, for commercial/research/educational use including without limitation use in instruction at your institution, sending it to specific colleagues that you know, and providing a copy to your institution's administrator.

All other uses, reproduction and distribution, including without limitation commercial reprints, selling or licensing copies or access, or posting on open internet sites, your personal or institution's website or repository, are requested to cite properly.

Digital Object Identifier: http://dx.doi.org/10.4172/2157-7412.1000115



Review Article

Open Access

Neurogenetics and Epigenetics in Impulsive Behaviour: Impact on Reward Circuitry

Trevor Archer¹, Marlene Oscar-Berman², Kenneth Blum^{3*} and Mark Gold³

¹Department of Psychology, University of Gothenburg, Box 500, SE-40530 Gothenburg, Sweden ²Departments of Psychiatry, Neurology, and Anatomy and Neurobiology, Boston University School of Medicine, and Boston VA Healthcare System, Boston, MA, USA ³Department of Psychiatry, University of Florida College of Medicine, and McKnight Brain Institute, Gainesville, FL, USA

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 a suscitated 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 environmentinduced, and it occurs during cell differentiation. In other words, nongenetic 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

*Corresponding author: Kenneth Blum, Department of Psychiatry, University of Florida, College of Medicine, PO Box 103424, Gainesville, Florida 32610-3424, USA, Tel: (352)392-3681; Fax:(352) 392- 9887; E-mail: Drd2gene@aol.com

Received March 17, 2012; Accepted May 28, 2012; Published May 30, 2012

Citation: Archer T, Oscar-Berman M, Blum K, Gold M (2012) Neurogenetics and Epigenetics in Impulsive Behaviour: Impact on Reward Circuitry. J Genet Syndr Gene Ther 3:115. doi:10.4172/2157-7412.1000115

Copyright: © 2012 Archer T, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

[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 healthpromoting 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 hypothalamicpituitary-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 cotwins, 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 acore 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

Page 3 of 15

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 hippocampuslinked 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 earlylife 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 selfcontrol, 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 cognitiveemotional 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 nonpsychopathic 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

Page 4 of 15

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 $\mathrm{HTR}_{_{\mathrm{IA}}}$ 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_{1,4}, 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 anxiousfearful 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 neurodevelopmentallyinappropriate 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 televisionwatching 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

Page 5 of 15

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 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 casecontrol 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 D1/D5 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 geneenvironment 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

Page 7 of 15

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-byenvironment 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, Val⁶⁶Met 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].

Page 8 of 15

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 biologicallyrelevant 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.

Acknowledgements

J Genet Syndr Gene Ther

The writing of this paper was supported in part by the US Department of Health and Human Services, NIAAA (R01 AA 07112, K05 AA 00219), and by the Medical Research Service of the US Department of Veterans Affairs.

- 1. Russo VEA (1996) Epigenetic mechanisms of gene regulation. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY.
- 2. Bird A (2007) Perceptions of epigenetics. Nature 447: 396-398.
- Reik W (2007) Stability and flexibility of epigenetic gene regulation in mammalian development. Nature 447: 425-432.
- Berger SL, Kouzarides T, Shiekhattar R, Shilatifard A (2009) An operational definition of epigenetics. Genes Dev 23: 781-783.
- Bale TL, Baram TZ, Brown AS, Goldstein JM, Insel TR, et al. (2010) Early life programming and neurodevelopmental disorders. Biol Psychiatry 68: 314-319.
- 6. Archer T, Blum K (2011) Epigenetics in neuropsychiatry. (1st edn). CRC Press.
- Ballas N, Grunseich C, Lu DD, Speh JC, Mandel G (2005) REST and its corepressors mediate plasticity of neuronal gene chromatin throughout neurogenesis. Cell 121: 645-657.
- Takizawa T, Nakashima K, Namihira M, Ochiai W, Uemura A, et al. (2001) DNA methylation is a critical cell-intrinsic determinant of astrocyte differentiation in the fetal brain. Dev Cell 1: 749-758.
- Ye F, Chen Y, Hoang T, Montgomery RL, Zhao XH, et al. (2009) HDAC1 and HDAC2 regulate oligodendrocyte differentiation by disrupting the beta-catenin-TCF interaction. Nat Neurosci 12: 829-838.
- Kim HJ, Leeds P, Chuang DM (2009) The HDAC inhibitor, sodium butyrate, stimulates neurogenesis in the ischemic brain. J Neurochem 110: 1226-1240.
- Mandel G, Fiondella CG, Covey MV, Lu DD, Loturco JJ, et al. (2011) Repressor element 1 silencing transcription factor (REST) controls radial migration and temporal neuronal specification during neocortical development. Proc Natl Acad Sci U S A 108: 16789-16794.
- Pittenger C, Kandel ER (2003) In search of general mechanisms for longlasting plasticity: Aplysia and the hippocampus. Philos Trans R Soc Lond B Biol Sci 358: 757-763.
- Whitlock JR, Heynen AJ, Shuler MG, Bear MF (2006) Learning induces longterm potentiation in the hippocampus. Science 313: 1093-1097.
- Sinn DI, Kim SJ, Chu K, Jung KH, Lee ST, et al. (2007) Valproic acid-mediated neuroprotection in intracerebral hemorrhage via histone deacetylase inhibition and transcriptional activation. Neurobiol Dis 26: 464-472.
- Eleuteri S, Monti B, Brignani S, Contestabile A (2009) Chronic dietary administration of valproic acid protects neurons of the rat nucleus basalis magnocellularis from ibotenic acid neurotoxicity. Neurotox Res 15: 127-132.
- Kim D, Frank CL, Dobbin MM, Tsunemoto RK, Tu W, et al. (2008) Deregulation of HDAC1 by p25/Cdk5 in neurotoxicity. Neuron 60: 803-817.
- Gräff J, Kim D, Dobbin MM, Tsai LH (2011) Epigenetic regulation of gene expression in physiological and pathological brain processes. Physiol Rev 91: 603-649.
- Lupien SJ, McEwen BS, Gunnar MR, Heim C (2009) Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat Rev Neurosci 10: 434-445.
- Drake AJ, Seckl JR (2011) Prenatal stress, glucocorticoids, and the metabolic syndrome. Obesity Before Birth 30: 279-300
- Archer T, Oscar-Berman M, Blum K (2011) Epigenetics in developmental disorder: ADHD and endophenotypes. J Genet Syndr Gene Ther 2: pii: 1000104.
- 21. Hariri AR (2010) Genetic polymorphisms: a cornerstone of translational biobehavioral research. Sci Transl Med 2: 18ps6.
- Chan KL, Tong KY, Yip SP (2008) Relationship of serum brain-derived neurotrophic factor (BDNF) and health-related lifestyle in healthy human subjects. Neurosci Lett 447: 124-128.
- Canani RB, Costanzo MD, Leone L, Bedogni G, Brambilla P, et al. (2011) Epigenetic mechanisms elicited by nutrition in early life. Nutr Res Rev 24: 198-205.
- 24. Dominguez-Salas P, Cox SE, Prentice AM, Hennig BJ, Moore SE (2012) Maternal nutritional status, C(1) metabolism and offspring DNA methylation: a review of current evidence in human subjects. Proc Nutr Soc 71: 154-165.

- 25. Konycheva G, Dziadek MA, Ferguson LR, Krägeloh CU, Coolen MW, et al. (2011) Dietary methyl donor deficiency during pregnancy in rats shapes learning and anxiety in offspring. Nutr Res 31: 790-804.
- 26. Branchi I, Francia N, Alleva E (2004) Epigenetic control of neurobehavioural plasticity: the role of neurotrophins. Behav Pharmacol 15: 353-362.
- 27. Previc FH (2007) Prenatal influences on brain dopamine and their relevance to the rising incidence of autism. Med Hypotheses 68: 46-60.
- Ouellet-Morin I, Odgers CL, Danese A, Bowes L, Shakoor S, et al. (2011) Blunted cortisol responses to stress signal social and behavioral problems among maltreated/bullied 12-year-old children. Biol Psychiatry 70: 1016-1023.
- Ouellet-Morin I, Danese A, Bowes L, Shakoor S, Ambler A, et al. (2011) A discordant monozygotic twin design shows blunted cortisol reactivity among bullied children. J Am Acad Child Adolesc Psychiatry 50: 574-582.
- Palomo T, Beninger RJ, Kostrzewa RM, Archer T (2008) Affective status in relation to impulsive, motor and motivational symptoms: personality, development and physical exercise. Neurotox Res 14: 151-168.
- Cosi S, Hernández-Martínez C, Canals J, Vigil-Colet A (2011) Impulsivity and internalizing disorders in childhood. Psychiatry Res 190: 342-347.
- Wittmann M, Simmons AN, Flagan T, Lane SD, Wackermann J, et al. (2011) Neural substrates of time perception and impulsivity. Brain Res 1406: 43-58.
- Jablonka E, Raz G (2009) Transgenerational epigenetic inheritance: prevalence, mechanisms, and implications for the study of heredity and evolution. Q Rev Biol 84: 131-176.
- 34. Nadeau JH (2009) Transgenerational genetic effects on phenotypic variation and disease risk. Hum Mol Genet 18: R202-210.
- 35. Vandegehuchte MB, Vandenbrouck T, Coninck DD, De Coen WM, Janssen CR (2010) Can metal stress induce transferable changes in gene transcription in Daphnia magna? Aquat Toxicol 97: 188-195.
- Foley DL, Craig JM, Morley R, Olsson CA, Dwyer T, et al. (2009) Prospects for epigenetic epidemiology. Am J Epidemiol 169: 389-400.
- Olsson CA, Foley DL, Parkinson-Bates M, Byrnes G, McKenzie M, et al. (2010) Prospects for epigenetic research within cohort studies of psychological disorder: a pilot investigation of a peripheral cell marker of epigenetic risk for depression. Biol Psychol 83: 159-165.
- Zhang TY, Meaney MJ (2010) Epigenetics and the environmental regulation of the genome and its function. Annu Rev Psychol 61: 439-466, C1-3.
- Weaver IC (2009) Shaping adult phenotypes through early life environments. Birth Defects Res C Embryo Today 87: 314-326.
- 40. Waterland RA (2009) Is epigenetics an important link between early life events and adult disease? Horm Res 71 Suppl 1: 13-16.
- Hochberg Z, Feil R, Constancia M, Fraga M, Junien C, et al. (2011) Child health, developmental plasticity, and epigenetic programming. Endocr Rev 32: 159-224.
- 42. Archer T, Kostrzewa RM, Palomo T, Beninger RJ (2010) Clinical staging in the pathophysiology of psychotic and affective disorders: facilitation of prognosis and treatment. Neurotox Res 18: 211-228.
- Waterland RA, Dolinoy DC, Lin JR, Smith CA, Shi X, et al. (2006) Maternal methyl supplements increase offspring DNA methylation at Axin Fused. Genesis 44: 401-406.
- 44. Gomes MV, Waterland RA (2008) Individual epigenetic variation: when, why, and so what? Nestle Nutr Workshop Ser Pediatr Program 62: 141-150.
- Waterland RA (2009) Early environmental effects on epigenetic regulation in humans. Epigenetics 4: 523-525.
- 46. Read J, Bentall RP, Fosse R (2009) Time to abandon the bio-bio-bio model of psychosis: Exploring the epigenetic and psychological mechanisms by which adverse life events lead to psychotic symptoms. Epidemiol Psichiatr Soc 18: 299-310.
- Narayan P, Dragunow M (2010) Pharmacology of epigenetics in brain disorders. Br J Pharmacol 159: 285-303.
- Priest NK, Wade MJ (2010) Maternal-zygotic epistasis and the evolution of genetic diseases. J Biomed Biotechnol 2010: 478732.
- 49. Montag C, Markett S, Basten U, Stelzel C, Fiebach C, et al. (2010) Epistasis

of the DRD2/ANKK1 Taq Ia and the BDNF Val66Met polymorphism impacts novelty seeking and harm avoidance. Neuropsychopharmacology 35: 1860-1867.

- Wells TT, Beevers CG, McGeary JE (2010) Serotonin transporter and BDNF genetic variants interact to predict cognitive reactivity in healthy adults. J Affect Disord 126: 223-229.
- Turetsky BI, Greenwood TA, Olincy A, Radant AD, Braff DL, et al. (2008) Abnormal auditory N100 amplitude: a heritable endophenotype in first-degree relatives of schizophrenia probands. Biol Psychiatry 64: 1051-1059.
- Archer T, Beninger RJ, Palomo T, Kostrzewa RM (2010) Epigenetics and biomarkers in the staging of neuropsychiatric disorders. Neurotox Res 18: 347-366.
- de Kloet ER, Fitzsimons CP, Datson NA, Meijer OC, Vreugdenhil E (2009) Glucocorticoid signaling and stress-related limbic susceptibility pathway: about receptors, transcription machinery and microRNA. Brain Res 1293: 129-141.
- Weaver IC (2009) Epigenetic effects of glucocorticoids. Semin Fetal Neonatal Med 14: 143-150.
- 55. Weaver IC, Diorio J, Seckl JR, Szyf M, Meaney MJ (2004) Early environmental regulation of hippocampal glucocorticoid receptor gene expression: characterization of intracellular mediators and potential genomic target sites. Ann N Y Acad Sci 1024: 182-212.
- Dedovic K, Rexroth M, Wolff E, Duchesne A, Scherling C, et al. (2009) Neural correlates of processing stressful information: an event-related fMRI study. Brain Res 1293: 49-60.
- Pruessner JC, Dedovic K, Pruessner M, Lord C, Buss C, et al. (2010) Stress regulation in the central nervous system: evidence from structural and functional neuroimaging studies in human populations - 2008 Curt Richter Award Winner. Psychoneuroendocrinology 35: 179-191.
- McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonté B, et al. (2009) Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nat Neurosci 12: 342-348.
- Khalili-Mahani N, Dedovic K, Engert V, Pruessner M, Pruessner JC (2010) Hippocampal activation during a cognitive task is associated with subsequent neuroendocrine and cognitive responses to psychological stress. Hippocampus 20: 323-334.
- Canli T, Qiu M, Omura K, Congdon E, Haas BW, et al. (2006) Neural correlates of epigenesis. Proc Natl Acad Sci U S A 103: 16033-16038.
- Gräff J, Mansuy IM (2009) Epigenetic dysregulation in cognitive disorders. Eur J Neurosci 30: 1-8.
- Quirin M, Pruessner JC, Kuhl J (2008) HPA system regulation and adult attachment anxiety: individual differences in reactive and awakening cortisol. Psychoneuroendocrinology 33: 581-590.
- Lahiri DK, Maloney B, Zawia NH (2009) The LEARn model: an epigenetic explanation for idiopathic neurobiological diseases. Mol Psychiatry 14: 992-1003.
- Palomo T, Kostrzewa RM, Beninger RJ, Archer T (2007) Treatment consideration and manifest complexity in comorbid neuropsychiatric disorders. Neurotox Res 12: 43-60.
- 65. Haden SC, Shiva A (2008) Trait impulsivity in a forensic inpatient sample: an evaluation of the Barratt impulsiveness scale. Behav Sci Law 26: 675-690.
- 66. Reynolds B (2006) A review of delay-discounting research with humans: relations to drug use and gambling. Behav Pharmacol 17: 651-667.
- 67. Palomo T, Beninger RJ, Kostrzewa RM, Archer T (2008) Focusing on symptoms rather than diagnoses in brain dysfunction: conscious and nonconscious expression in impulsiveness and decision-making. Neurotox Res 14: 1-20.
- Miller DJ, Vachon DD, Lynam DR (2009) Neuroticism, Negative Affect, and Negative Affect Instability: Establishing Convergent and Discriminant Validity Using Ecological Momentary Assessment. Pers Individ Dif 47: 873-877.
- Dolan M, Deakin WJ, Roberts N, Anderson I (2002) Serotonergic and cognitive impairment in impulsive aggressive personality disordered offenders: are there implications for treatment? Psychol Med 32: 105-117.
- Peluso MA, Hatch JP, Glahn DC, Monkul ES, Sanches M, et al. (2007) Trait impulsivity in patients with mood disorders. J Affect Disord 100: 227-231.

Page 11 of 15

- Keilp JG, Sackeim HA, Mann JJ (2005) Correlates of trait impulsiveness in performance measures and neuropsychological tests. Psychiatry Res 135: 191-201.
- 72. Rogers RD (2003) Neuropsychological investigations of the impulsive personality disorders. Psychol Med 33: 1335-1340.
- Dolan M, Park I (2002) The neuropsychology of antisocial personality disorder. Psychol Med 32: 417-427.
- 74. Harrison EL, Coppola S, McKee SA (2009) Nicotine deprivation and trait impulsivity affect smokers' performance on cognitive tasks of inhibition and attention. Exp Clin Psychopharmacol 17: 91-98.
- Potter AS, Newhouse PA (2004) Effects of acute nicotine administration on behavioral inhibition in adolescents with attention-deficit/hyperactivity disorder. Psychopharmacology (Berl) 176: 182-194.
- Barratt ES, Stanford MS, Kent TA, Felthous A (1997) Neuropsychological and cognitive psychophysiological substrates of impulsive aggression. Biol Psychiatry 41: 1045-1061.
- Beck A, Schlagenhauf F, Wüstenberg T, Hein J, Kienast T, et al. (2009) Ventral striatal activation during reward anticipation correlates with impulsivity in alcoholics. Biol Psychiatry 66: 734-742.
- Frank MJ, Claus ED (2006) Anatomy of a decision: striato-orbitofrontal interactions in reinforcement learning, decision making, and reversal. Psychol Rev 113: 300-326.
- Rustichini A (2005) Neuroscience. Emotion and reason in making decisions. Science 310: 1624-1625.
- Koenigs M, Tranel D (2007) Irrational economic decision-making after ventromedial prefrontal damage: evidence from the Ultimatum Game. J Neurosci 27: 951-956.
- Racine SE, Culbert KM, Larson CL, Klump KL (2009) The possible influence of impulsivity and dietary restraint on associations between serotonin genes and binge eating. J Psychiatr Res 43: 1278-1286.
- Silva H, Iturra P, Solari A, Villarroel J, Jerez S, et al. (2010) Fluoxetine response in impulsive-aggressive behavior and serotonin transporter polymorphism in personality disorder. Psychiatr Genet 20: 25-30.
- 83. Lowry CA, Hale MW, Evans AK, Heerkens J, Staub DR, et al. (2008) Serotonergic systems, anxiety, and affective disorder: focus on the dorsomedial part of the dorsal raphe nucleus. Ann N Y Acad Sci 1148: 86-94.
- Murakami H, Matsunaga M, Ohira H (2009) Association of serotonin transporter gene polymorphism and emotion regulation. Neuroreport 20: 414-418.
- Lee R, Coccaro E (2007) Neurobiology of impulsive aggression: focus on serotonin and the orbitofrontal cortex. Cambridge University Press, New York, NY.
- Zouk H, Tousignant M, Seguin M, Lesage A, Turecki G (2006) Characterization of impulsivity in suicide completers: clinical, behavioral and psychosocial dimensions. J Affect Disord 92: 195-204.
- Pezawas L, Meyer-Lindenberg A, Goldman AL, Verchinski BA, Chen G, et al. (2008) Evidence of biologic epistasis between BDNF and SLC6A4 and implications for depression. Mol Psychiatry 13: 709-716.
- Philibert R, Madan A, Andersen A, Cadoret R, Packer H, et al. (2007) Serotonin transporter mRNA levels are associated with the methylation of an upstream CpG island. Am J Med Genet B Neuropsychiatr Genet 144B: 101-105.
- Philibert RA, Sandhu H, Hollenbeck N, Gunter T, Adams W, et al. (2008) The relationship of 5HTT (SLC6A4) methylation and genotype on mRNA expression and liability to major depression and alcohol dependence in subjects from the lowa Adoption Studies. Am J Med Genet B Neuropsychiatr Genet 147B: 543-549.
- Williams RB, Marchuk DA, Gadde KM, Barefoot JC, Grichnik K, et al. (2003) Serotonin-related gene polymorphisms and central nervous system serotonin function. Neuropsychopharmacology 28: 533-541.
- Benko A, Lazary J, Molnar E, Gonda X, Tothfalusi L, et al. (2010) Significant association between the C(-1019)G functional polymorphism of the HTR1A gene and impulsivity. Am J Med Genet B Neuropsychiatr Genet 153B: 592-599.
- Stoltenberg SF, Batien BD, Birgenheir DG (2008) Does gender moderate associations among impulsivity and health-risk behaviors? Addict Behav 33: 252-265.

- Stoltenberg SF, Nag P (2010) Description and validation of a dynamical systems model of presynaptic serotonin function: genetic variation, brain activation and impulsivity. Behav Genet 40: 262-279.
- 94. Murphy SE, Longhitano C, Ayres RE, Cowen PJ, Harmer CJ, et al. (2009) The role of serotonin in nonnormative risky choice: the effects of tryptophan supplements on the "reflection effect" in healthy adult volunteers. J Cogn Neurosci 21: 1709-1719.
- Walderhaug E, Lunde H, Nordvik JE, Landrø NI, Refsum H, et al. (2002) Lowering of serotonin by rapid tryptophan depletion increases impulsiveness in normal individuals. Psychopharmacology (Berl) 164: 385-391.
- Walderhaug E, Magnusson A, Neumeister A, Lappalainen J, Lunde H, et al. (2007) Interactive effects of sex and 5-HTTLPR on mood and impulsivity during tryptophan depletion in healthy people. Biol Psychiatry 62: 593-599.
- Walderhaug E, Landrø NI, Magnusson A (2008) A synergic effect between lowered serotonin and novel situations on impulsivity measured by CPT. J Clin Exp Neuropsychol 30: 204-211.
- Jollant F, Buresi C, Guillaume S, Jaussent I, Bellivier F, et al. (2007) The influence of four serotonin-related genes on decision-making in suicide attempters. Am J Med Genet B Neuropsychiatr Genet 144B: 615-624.
- Must A, Juhász A, Rimanóczy A, Szabó Z, Kéri S, et al. (2007) Major depressive disorder, serotonin transporter, and personality traits: why patients use suboptimal decision-making strategies? J Affect Disord 103: 273-276.
- 100.Juhasz G, Downey D, Hinvest N, Thomas E, Chase D, et al. (2010) Risk-taking behavior in a gambling task associated with variations in the tryptophan hydroxylase 2 gene: relevance to psychiatric disorders. Neuropsychopharmacology 35: 1109-1119.
- 101.Lampe K, Konrad K, Kroener S, Fast K, Kunert HJ, et al. (2007) Neuropsychological and behavioural disinhibition in adult ADHD compared to borderline personality disorder. Psychol Med 37: 1717-1729.
- 102. Blum K, Sheridan PJ, Wood RC, Braverman ER, Chen TJ, et al. (1996) The D2 dopamine receptor gene as a determinant of reward deficiency syndrome. J R Soc Med 89: 396-400.
- 103. Blum K, Chen AL, Oscar-Berman M, Chen TJ, Lubar J, et al. (2011) Generational association studies of dopaminergic genes in reward deficiency syndrome (RDS) subjects: selecting appropriate phenotypes for reward dependence behaviors. Int J Environ Res Public Health 8: 4425-4459.
- 104.Bowirrat A, Oscar-Berman M (2005) Relationship between dopaminergic neurotransmission, alcoholism, and Reward Deficiency syndrome. Am J Med Genet B Neuropsychiatr Genet 132B: 29-37.
- 105. Reif A, Herterich S, Strobel A, Ehlis AC, Saur D, et al. (2006) A neuronal nitric oxide synthase (NOS-I) haplotype associated with schizophrenia modifies prefrontal cortex function. Mol Psychiatry 11: 286-300.
- 106. Reif A, Jacob CP, Rujescu D, Herterich S, Lang S, et al. (2009) Influence of functional variant of neuronal nitric oxide synthase on impulsive behaviors in humans. Arch Gen Psychiatry 66: 41-50.
- 107. Retz W, Reif A, Freitag CM, Retz-Junginger P, Rösler M (2010) Association of a functional variant of neuronal nitric oxide synthase gene with self-reported impulsiveness, venturesomeness and empathy in male offenders. J Neural Transm 117: 321-324.
- 108. Eisenberg N (2000) Emotion, regulation, and moral development. Annu Rev Psychol 51: 665-697.
- 109. Eysenck S, Daum I, Schugens M (1990) A cross-cultural study of impulsiveness, venturesomeness and empathy: Germany and England. Zeitschrift für Differentielle und Diagnostische Psychologie 11: 209-213.
- 110. Jacob CP, Nguyen TT, Dempfle A, Heine M, Windemuth-Kieselbach C, et al. (2010) A gene-environment investigation on personality traits in two independent clinical sets of adult patients with personality disorder and attention deficit/hyperactive disorder. Eur Arch Psychiatry Clin Neurosci 260: 317-326.
- 111. Baarendse PJ, Vanderschuren LJ (2012) Dissociable effects of monoamine reuptake inhibitors on distinct forms of impulsive behavior in rats. Psychopharmacology (Berl) 219: 313-326.
- 112. Wilbertz G, van Elst LT, Delgado MR, Maier S, Feige B, et al. (2012) Orbitofrontal reward sensitivity and impulsivity in adult attention deficit hyperactivity disorder. Neuroimage 60: 353-361.

- Barkley RA, Fischer M, Smallish L, Fletcher K (2006) Young adult outcome of hyperactive children: adaptive functioning in major life activities. J Am Acad Child Adolesc Psychiatry 45: 192-202.
- 114. Geissler J, Lesch KP (2011) A lifetime of attention-deficit/hyperactivity disorder: diagnostic challenges, treatment and neurobiological mechanisms. Expert Rev Neurother 11: 1467-1484.
- 115. Guldberg-Kjar T, Johansson B (2009) Old people reporting childhood AD/HD symptoms: Retrospectively self-rated AD/HD symptoms in a population-based Swedish sample aged 65-80. Nord J Psychiatry.
- 116. Derks EM, Hudziak JJ, Dolan CV, van Beijsterveldt TC, Verhulst FC, et al. (2008) Genetic and environmental influences on the relation between attention problems and attention deficit hyperactivity disorder. Behav Genet 38: 11-23.
- 117. Elia J, Laracy S, Allen J, Nissley-Tsiopinis J, Borgmann-Winter K (2012) Epigenetics: genetics versus life experiences. Curr Top Behav Neurosci 9: 317-340.
- 118. Galéra C, Côté SM, Bouvard MP, Pingault JB, Melchior M, et al. (2011) Early risk factors for hyperactivity-impulsivity and inattention trajectories from age 17 months to 8 years. Arch Gen Psychiatry 68: 1267-1275.
- 119. Cirulli F, Berry A, Bonsignore LT, Capone F, D'Andrea I, et al. (2010) Early life influences on emotional reactivity: evidence that social enrichment has greater effects than handling on anxiety-like behaviors, neuroendocrine responses to stress and central BDNF levels. Neurosci Biobehav Rev 34: 808-820.
- 120.Post RM (2010) Mechanisms of illness progression in the recurrent affective disorders. Neurotox Res 18: 256-271.
- 121.Nikolas M, Friderici K, Waldman I, Jernigan K, Nigg JT (2010) Gene x environment interactions for ADHD: synergistic effect of 5HTTLPR genotype and youth appraisals of inter-parental conflict. Behav Brain Funct 6: 23.
- 122. Franc N, Maury M, Purper-Ouakil D (2009) [ADHD and attachment processes: are they related?]. Encephale 35: 256-261.
- 123.Martel MM (2009) Research review: a new perspective on attention-deficit/ hyperactivity disorder: emotion dysregulation and trait models. J Child Psychol Psychiatry 50: 1042-1051.
- 124. Harty SC, Miller CJ, Newcorn JH, Halperin JM (2009) Adolescents with childhood ADHD and comorbid disruptive behavior disorders: aggression, anger, and hostility. Child Psychiatry Hum Dev 40: 85-97.
- 125. Lahey BB, Loeber R, Burke JD, Applegate B (2005) Predicting future antisocial personality disorder in males from a clinical assessment in childhood. J Consult Clin Psychol 73: 389-399.
- 126. Tarter R, Vanyukov M, Giancola P, Dawes M, Blackson T, et al. (1999) Etiology of early age onset substance use disorder: a maturational perspective. Dev Psychopathol 11: 657-683.
- 127. Flory JD, Pytte CL, Hurd Y, Ferrell RE, Manuck SB (2011) Alcohol dependence, disinhibited behavior and variation in the prodynorphin gene. Biol Psychol 88: 51-56.
- 128. Blum K, Briggs AH, Elston SF, DeLallo L, Sheridan PJ, et al. (1982) Reduced leucine-enkephalin--like immunoreactive substance in hamster basal ganglia after long-term ethanol exposure. Science 216: 1425-1427.
- 129.Blum K, Elston SF, DeLallo L, Briggs AH, Wallace JE (1983) Ethanol acceptance as a function of genotype amounts of brain [Met]enkephalin. Proc Natl Acad Sci U S A 80: 6510-6512.
- Slutske WS, Zhu G, Meier MH, Martin NG (2010) Genetic and environmental influences on disordered gambling in men and women. Arch Gen Psychiatry 67: 624-630.
- 131. Slutske WS, Zhu G, Meier MH, Martin NG (2011) Disordered gambling as defined by the Diagnostic and Statistical Manual of Mental Disorders and the South Oaks Gambling Screen: evidence for a common etiologic structure. J Abnorm Psychol 120: 743-751.
- 132. Wölfling K, Bühler M, Leménager T, Mörsen C, Mann K (2009) [Gambling and internet addiction: review and research agenda]. Nervenarzt 80: 1030-1039.
- 133.Comings DE, Rosenthal RJ, Lesieur HR, Rugle LJ, Muhleman D, et al. (1996) A study of the dopamine D2 receptor gene in pathological gambling. Pharmacogenetics 6: 223-234.
- 134.Lobo DS, Souza RP, Tong RP, Casey DM, Hodgins DC, et al. (2010)

Association of functional variants in the dopamine D2-like receptors with risk for gambling behaviour in healthy Caucasian subjects. Biol Psychol 85: 33-37.

- 135. Kim SH, Baik SH, Park CS, Kim SJ, Choi SW, et al. (2011) Reduced striatal dopamine D2 receptors in people with Internet addiction. Neuroreport 22: 407-411.
- 136.Blum K, Gold MS (2011) Neuro-chemical activation of brain reward mesolimbic circuitry is associated with relapse prevention and drug hunger: a hypothesis. Med Hypotheses 76: 576-584.
- 137.Han DH, Hwang JW, Renshaw PF (2010) Bupropion sustained release treatment decreases craving for video games and cue-induced brain activity in patients with Internet video game addiction. Exp Clin Psychopharmacol 18: 297-304.
- 138.Lee YS, Han DH, Yang KC, Daniels MA, Na C, et al. (2008) Depression like characteristics of 5HTTLPR polymorphism and temperament in excessive internet users. J Affect Disord 109: 165-169.
- 139. Huber R, Kravitz EA (2010) Aggression: towards an integration of gene, brain and behaviour. (1st edn). Cambridge University Press.
- 140. Wahlund K, Kristiansson M (2009) Aggression, psychopathy and brain imaging - Review and future recommendations. Int J Law Psychiatry 32: 266-271.
- 141. Chen TJH, Blum K, Mathews D, Fisher L, Schnautz N, et al. (2007) Preliminary association of both the dopamine D2 receptor (DRD2) [Taq1 A1 allele] and the dopamine transporter (DAT1) [480 bp allele] genes with pathologicalaggressive behavior, a clinical subtype of Reward Deficiency Syndrome (RDS) in adolescents. Gene Ther Mol Biol 11: 93-112
- 142. Reuter J, Raedler T, Rose M, Hand I, Gläscher J, et al. (2005) Pathological gambling is linked to reduced activation of the mesolimbic reward system. Nat Neurosci 8: 147-148.
- 143. Vaske J, Wright JP, Beaver KM (2011) A dopamine gene (DRD2) distinguishes between offenders who have and have not been violently victimized. Int J Offender Ther Comp Criminol 55: 251-267.
- 144. Retz W, Rösler M, Supprian T, Retz-Junginger P, Thome J (2003) Dopamine D3 receptor gene polymorphism and violent behavior: relation to impulsiveness and ADHD-related psychopathology. J Neural Transm 110: 561-572.
- 145. Pavlov KA, Chistiakov DA, Chekhonin VP (2012) Genetic determinants of aggression and impulsivity in humans. J Appl Genet 53: 61-82.
- 146.Balaban E, Alper JS, Kasamon YL (1996) Mean genes and the biology of aggression: a critical review of recent animal and human research. J Neurogenet 11: 1-43.
- 147. Manuck SB, Flory JD, Ferrell RE, Mann JJ, Muldoon MF (2000) A regulatory polymorphism of the monoamine oxidase-A gene may be associated with variability in aggression, impulsivity, and central nervous system serotonergic responsivity. Psychiatry Res 95: 9-23.
- 148. Thalmeier A, Dickmann M, Giegling I, Schneider B, M Hartmann A, et al. (2008) Gene expression profiling of post-mortem orbitofrontal cortex in violent suicide victims. Int J Neuropsychopharmacol 11: 217-228.
- 149. Freimuth M, Moniz S, Kim SR (2011) Clarifying exercise addiction: differential diagnosis, co-occurring disorders, and phases of addiction. Int J Environ Res Public Health 8: 4069-4081.
- 150. de Mathis MA, de Alvarenga P, Funaro G, Torresan RC, Moraes I, et al. (2011) Gender differences in obsessive-compulsive disorder: a literature review. Rev Bras Psiquiatr 33: 390-399.
- 151.Claes L, Jiménez-Murcia S, Agüera Z, Castro R, Sánchez I, et al. (2011) Male Eating Disorder Patients With and Without Non-suicidal Self-injury: A Comparison of Psychopathological and Personality Features. Eur Eat Disord Rev.
- 152.Fernández-Aranda F, Jiménez-Murcia S, Alvarez-Moya EM, Granero R, Vallejo J, et al. (2006) Impulse control disorders in eating disorders: clinical and therapeutic implications. Compr Psychiatry 47: 482-488.
- 153. Vallelunga A, Flaibani R, Formento-Dojot P, Biundo R, Facchini S, et al. (2012) Role of genetic polymorphisms of the dopaminergic system in Parkinson's disease patients with impulse control disorders. Parkinsonism Relat Disord 18: 397-399.
- 154.Vilas D, Pont-Sunyer C, Tolosa E (2012) Impulse control disorders in Parkinson's disease. Parkinsonism Relat Disord 18 Suppl 1: S80-84.

- 155. Hudson JI, Pope HG Jr (2007) Genetic epidemiology of eating disorders and co-occurring conditions: the role of endophenotypes. Int J Eat Disord 40 Suppl: S76-78.
- 156. Spindler A, Milos G (2007) Links between eating disorder symptom severity and psychiatric comorbidity. Eat Behav 8: 364-373.
- 157. Forcano L, Alvarez E, Santamaría JJ, Jimenez-Murcia S, Granero R, et al. (2011) Suicide attempts in anorexia nervosa subtypes. Compr Psychiatry 52: 352-358.
- 158. Tchanturia K, Liao PC, Forcano L, Fernández-Aranda F, Uher R, et al. (2012) Poor decision making in male patients with anorexia nervosa. Eur Eat Disord Rev 20: 169-173.
- 159. Adambegan M, Wagner G, Nader IW, Fernandez-Aranda F, Treasure J, et al. (2012) Internalizing and externalizing behaviour problems in childhood contribute to the development of anorexia and bulimia nervosa-a study comparing sister pairs. Eur Eat Disord Rev 20: 116-120.
- 160. Van Camp JK, Beckers S, Zegers D, Verrijken A, Van Gaal LF, et al. (2012) Genetic association between WNT10B polymorphisms and obesity in a Belgian case-control population is restricted to males. Mol Genet Metab 105: 489-493.
- 161. Frieling H, Gozner A, Römer KD, Lenz B, Bönsch D, et al. (2007) Global DNA hypomethylation and DNA hypermethylation of the alpha synuclein promoter in females with anorexia nervosa. Mol Psychiatry 12: 229-230.
- 162. Frieling H, Bleich S, Otten J, Römer KD, Kornhuber J, et al. (2008) Epigenetic downregulation of atrial natriuretic peptide but not vasopressin mRNA expression in females with eating disorders is related to impulsivity. Neuropsychopharmacology 33: 2605-2609.
- 163. Frieling H, Albrecht H, Jedtberg S, Gozner A, Lenz B, et al. (2009) Elevated cannabinoid 1 receptor mRNA is linked to eating disorder related behavior and attitudes in females with eating disorders. Psychoneuroendocrinology 34: 620-624.
- 164. Ehrlich S, Weiss D, Burghardt R, Infante-Duarte C, Brockhaus S, et al. (2010) Promoter specific DNA methylation and gene expression of POMC in acutely underweight and recovered patients with anorexia nervosa. J Psychiatr Res 44: 827-833.
- 165. Campbell IC, Mill J, Uher R, Schmidt U (2011) Eating disorders, geneenvironment interactions and epigenetics. Neurosci Biobehav Rev 35: 784-793.
- 166. Prior LJ, Armitage JA (2009) Neonatal overfeeding leads to developmental programming of adult obesity: you are what you ate. J Physiol 587: 2419.
- 167.Sadri-Vakili G, Kumaresan V, Schmidt HD, Famous KR, Chawla P, et al. (2010) Cocaine-induced chromatin remodeling increases brain-derived neurotrophic factor transcription in the rat medial prefrontal cortex, which alters the reinforcing efficacy of cocaine. J Neurosci 30: 11735-11744.
- 168. Sun H, Cocker PJ, Zeeb FD, Winstanley CA (2012) Chronic atomoxetine treatment during adolescence decreases impulsive choice, but not impulsive action, in adult rats and alters markers of synaptic plasticity in the orbitofrontal cortex. Psychopharmacology (Berl.) 219: 285-301.
- 169.Bergman O, Westberg L, Lichtenstein P, Eriksson E, Larsson H (2011) Study on the possible association of brain-derived neurotrophic factor polymorphism with the developmental course of symptoms of attention deficit and hyperactivity. Int J Neuropsychopharmacol 14: 1367-1376.
- 170. Gatt JM, Nemeroff CB, Dobson-Stone C, Paul RH, Bryant RA, et al. (2009) Interactions between BDNF Val66Met polymorphism and early life stress predict brain and arousal pathways to syndromal depression and anxiety. Mol Psychiatry 14: 681-695.
- 171. Wagner S, Baskaya Ö, Dahmen N, Lieb K, Tadic A (2010) Modulatory role of the brain-derived neurotrophic factor Val66Met polymorphism on the effects of serious life events on impulsive aggression in borderline personality disorder. Genes Brain Behav 9: 97-102.
- 172.Bernier A, Carlson SM, Bordeleau S, Carrier J (2010) Relations between physiological and cognitive regulatory systems: infant sleep regulation and subsequent executive functioning. Child Dev 81: 1739-1752.
- 173.Fontes MA, Bolla KI, Cunha PJ, Almeida PP, Jungerman F, et al. (2011) Cannabis use before age 15 and subsequent executive functioning. Br J Psychiatry 198: 442-447.

174.Pharo H, Sim C, Graham M, Gross J, Hayne H (2011) Risky business: executive function, personality, and reckless behavior during adolescence and emerging adulthood. Behav Neurosci 125: 970-978.

Page 13 of 15

- 175.Ledgerwood DM, Orr ES, Kaploun KA, Milosevic A, Frisch GR, et al. (2012) Executive function in pathological gamblers and healthy controls. J Gambl Stud 28: 89-103.
- 176. Nakazato M, Tchanturia K, Schmidt U, Campbell IC, Treasure J, et al. (2009) Brain-derived neurotrophic factor (BDNF) and set-shifting in currently ill and recovered anorexia nervosa (AN) patients. Psychol Med 39: 1029-1035.
- 177.Nakazato M, Hashimoto K, Schmidt U, Tchanturia K, Campbell IC, et al. (2010) Serum glutamine, set-shifting ability and anorexia nervosa. Ann Gen Psychiatry 9: 29-29.
- Nathan PJ, O'Neill BV, Napolitano A, Bullmore ET (2011) Neuropsychiatric adverse effects of centrally acting antiobesity drugs. CNS Neurosci Ther 17: 490-505.
- 179. Bailer UF, Frank GK, Henry SE, Price JC, Meltzer CC, et al. (2007) Serotonin transporter binding after recovery from eating disorders. Psychopharmacology (Berl) 195: 315-324.
- 180. Passamonti L, Fera F, Magariello A, Cerasa A, Gioia MC, et al. (2006) Monoamine oxidase-a genetic variations influence brain activity associated with inhibitory control: new insight into the neural correlates of impulsivity. Biol Psychiatry 59: 334-340.
- Sellman D (2010) Ten things the alcohol industry won't tell you about alcohol. Drug Alcohol Rev 29: 301-303.
- 182. Goldstein RZ, Volkow ND (2011) Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. Nat Rev Neurosci 12: 652-669.
- 183. Oscar-Berman M (2012) Function and Dysfunction of Prefrontal Brain Circuitry in Alcoholic Korsakoff's Syndrome. Neuropsychol Rev.
- 184.McQuown SC, Wood MA (2010) Epigenetic regulation in substance use disorders. Curr Psychiatry Rep 12: 145-153.
- 185. Robles E, Huang BE, Simpson PM, McMillan DE (2011) Delay discounting, impulsiveness, and addiction severity in opioid-dependent patients. J Subst Abuse Treat 41: 354-362.
- 186. Fontenelle LF, Oostermeijer S, Harrison BJ, Pantelis C, Yücel M (2011) Obsessive-compulsive disorder, impulse control disorders and drug addiction: common features and potential treatments. Drugs 71: 827-840.
- 187. Alvarez-Moya EM, Ochoa C, Jiménez-Murcia S, Aymamí MN, Gómez-Peña M, et al. (2011) Effect of executive functioning, decision-making and self-reported impulsivity on the treatment outcome of pathologic gambling. J Psychiatry Neurosci 36: 165-175.
- 188. Crews FT, Boettiger CA (2009) Impulsivity, frontal lobes and risk for addiction. Pharmacol Biochem Behav 93: 237-247.
- 189. Pine A, Shiner T, Seymour B, Dolan RJ (2010) Dopamine, time, and impulsivity in humans. J Neurosci 30: 8888-8896.
- 190.Renthal W, Nestler EJ (2008) Epigenetic mechanisms in drug addiction. Trends Mol Med 14: 341-350.
- 191.Maze I, Feng J, Wilkinson MB, Sun H, Shen L, et al. (2011) Cocaine dynamically regulates heterochromatin and repetitive element unsilencing in nucleus accumbens. Proc Natl Acad Sci U S A 108: 3035-3040.
- 192.Mao LM, Horton E, Guo ML, Xue B, Jin DZ, et al. (2011) Cocaine increases phosphorylation of MeCP2 in the rat striatum in vivo: a differential role of NMDA receptors. Neurochem Int 59: 610-617.
- 193.Maze I, Russo SJ (2010) Transcriptional mechanisms: underlying addictionrelated structural plasticity. Mol Interv 10: 219-230.
- 194.Buscemi L, Turchi C (2011) An overview of the genetic susceptibility to alcoholism. Med Sci Law 51 Suppl 1: S2-6.
- 195. Alegría-Torres JA, Baccarelli A, Bollati V (2011) Epigenetics and lifestyle. Epigenomics 3: 267-277.
- 196. Qiang M, Denny A, Lieu M, Carreon S, Li J (2011) Histone H3K9 modifications are a local chromatin event involved in ethanol-induced neuroadaptation of the NR2B gene. Epigenetics 6.
- 197. Zhang FF, Cardarelli R, Carroll J, Fulda KG, Kaur M, et al. (2011) Significant

differences in global genomic DNA methylation by gender and race/ethnicity in peripheral blood. Epigenetics 6: 623-629.

- 198.Pinto E, Ansseau M (2009) [Genetic factors of alcohol-dependence]. Encephale 35: 461-469.
- 199. Gluckman PD, Hanson MA, Low FM (2011) The role of developmental plasticity and epigenetics in human health. Birth Defects Res C Embryo Today 93: 12-18.
- 200. Lobanenkov V, Loukinov D, Pugacheva E (2011) Environmental epigenomics and disease susceptibility. Keystone symposia on molecular and cellular biology. The Grove Park Hotel & Spa, Ashville, NC, USA, 27 March–1 April 2011. Epigenomics 3: 261-266.
- 201. Van den Bergh BR (2011) Developmental programming of early brain and behaviour development and mental health: a conceptual framework. Dev Med Child Neurol 53 Suppl 4: 19-23.
- 202. Perera F, Herbstman J (2011) Prenatal environmental exposures, epigenetics, and disease. Reprod Toxicol 31: 363-373.
- 203. DiNieri JA, Wang X, Szutorisz H, Spano SM, Kaur J, et al. (2011) Maternal cannabis use alters ventral striatal dopamine D2 gene regulation in the offspring. Biol Psychiatry 70: 763-769.
- 204. Cangemi S, Giorgi I, Bonfiglio NS, Renati R, Vittadini G (2010) Impulsiveness and time perception in alcohol dependent patients in alcoholic rehabilitation treatment. G Ital Med Lav Ergon 32: B23-28.
- 205. Jakubczyk A, Klimkiewicz A, Topolewska-Wochowska A, Serafin P, Sadowska-Mazuryk J, et al. (2012) Relationships of impulsiveness and depressive symptoms in alcohol dependence. J Affect Disord 136: 841-847.
- 206. Jakubczyk A, Wrzosek M, Lukaszkiewicz J, Sadowska-Mazuryk J, Matsumoto H, et al. (2012) The CC genotype in HTR2A T102C polymorphism is associated with behavioral impulsivity in alcohol-dependent patients. J Psychiatr Res 46: 44-49.
- 207.Krishnan HR, Al-Hasan YM, Pohl JB, Ghezzi A, Atkinson NS (2012) A role for dynamin in triggering ethanol tolerance. Alcohol Clin Exp Res 36: 24-34.
- 208.Lydall GJ, Bass NJ, McQuillin A, Lawrence J, Anjorin A, et al. (2011) Confirmation of prior evidence of genetic susceptibility to alcoholism in a genome-wide association study of comorbid alcoholism and bipolar disorder. Psychiatr Genet 21: 294-306.
- 209. Zuo L, Gelernter J, Zhang CK, Zhao H, Lu L, et al. (2012) Genome-wide association study of alcohol dependence implicates KIAA0040 on chromosome 1q. Neuropsychopharmacology 37: 557-566.
- 210. Shim SH, Hwangbo Y, Kwon YJ, Jeong HY, Lee BH, et al. (2008) Increased levels of plasma brain-derived neurotrophic factor (BDNF) in children with attention deficit-hyperactivity disorder (ADHD). Prog Neuropsychopharmacol Biol Psychiatry 32: 1824-1828.
- Cho SC, Kim HW, Kim BN, Kim JW, Shin MS, et al. (2010) Gender-specific association of the brain-derived neurotrophic factor gene with attention-deficit/ hyperactivity disorder. Psychiatry Investig 7: 285-290.
- 212. Oades RD, Lasky-Su J, Christiansen H, Faraone SV, Sonuga-Barke EJ, et al. (2008) The influence of serotonin- and other genes on impulsive behavioral aggression and cognitive impulsivity in children with attention-deficit/ hyperactivity disorder (ADHD): findings from a family-based association test (FBAT) analysis. Behav Brain Funct 4: 48.
- 213. Gratacòs M, González JR, Mercader JM, de Cid R, Urretavizcaya M, et al. (2007) Brain-derived neurotrophic factor Val66Met and psychiatric disorders: meta-analysis of case-control studies confirm association to substance-related disorders, eating disorders, and schizophrenia. Biol Psychiatry 61: 911-922.
- Russo-Neustadt A (2003) Brain-derived neurotrophic factor, behavior, and new directions for the treatment of mental disorders. Semin Clin Neuropsychiatry 8: 109-118.
- 215. Tapia-Arancibia L, Rage F, Givalois L, Arancibia S (2004) Physiology of BDNF: focus on hypothalamic function. Front Neuroendocrinol 25: 77-107.
- 216.Araya AV, Orellana X, Espinoza J (2008) Evaluation of the effect of caloric restriction on serum BDNF in overweight and obese subjects: preliminary evidences. Endocrine 33: 300-304.
- 217.Arija V, Ferrer-Barcala M, Aranda N, Canals J (2010) BDNF Val66Met polymorphism, energy intake and BMI: a follow-up study in schoolchildren at risk of eating disorders. BMC Public Health 10: 363.

218.Lebrun B, Bariohay B, Moyse E, Jean A (2006) Brain-derived neurotrophic factor (BDNF) and food intake regulation: a minireview. Auton Neurosci 126-127: 30-8.

Page 14 of 15

- 219. Mercader JM, Fernández-Aranda F, Gratacòs M, Ribasés M, Badía A, et al. (2007) Blood levels of brain-derived neurotrophic factor correlate with several psychopathological symptoms in anorexia nervosa patients. Neuropsychobiology 56: 185-190.
- 220. Archer T, Kostrzewa RM (2012) Physical exercise alleviates ADHD symptoms: regional deficits and development trajectory. Neurotox Res 21: 195-209.
- 221. Minelli A, Zanardini R, Bonvicini C, Sartori R, Pedrini L, et al. (2011) BDNF serum levels, but not BDNF Val66Met genotype, are correlated with personality traits in healthy subjects. Eur Arch Psychiatry Clin Neurosci 261: 323-329.
- 222. Hariri AR, Goldberg TE, Mattay VS, Kolachana BS, Callicott JH, et al. (2003) Brain-derived neurotrophic factor val66met polymorphism affects human memory-related hippocampal activity and predicts memory performance. J Neurosci 23: 6690-6694.
- 223.Beckers S, Peeters A, Zegers D, Mertens I, Van Gaal L, et al. (2008) Association of the BDNF Val66Met variation with obesity in women. Mol Genet Metab 95: 110-112.
- 224. Friedel S, Horro FF, Wermter AK, Geller F, Dempfle A, et al. (2005) Mutation screen of the brain derived neurotrophic factor gene (BDNF): identification of several genetic variants and association studies in patients with obesity, eating disorders, and attention-deficit/hyperactivity disorder. Am J Med Genet B Neuropsychiatr Genet 132B: 96-99.
- 225. Han JC, Liu QR, Jones M, Levinn RL, Menzie CM, et al. (2008) Brain-derived neurotrophic factor and obesity in the WAGR syndrome. N Engl J Med 359: 918-927.
- 226. Skledar M, Nikolac M, Dodig-Curkovic K, Curkovic M, Borovecki F, et al. (2011) Association between brain-derived neurotrophic factor Val66Met and obesity in children and adolescents. Prog Neuropsychopharmacol Biol Psychiatry 36: 136-140.
- 227.Timpano KR, Schmidt NB, Wheaton MG, Wendland JR, Murphy DL (2011) Consideration of the BDNF gene in relation to two phenotypes: hoarding and obesity. J Abnormal Psychol 120: 700-707.
- 228.Kumsta R, Kreppner J, Rutter M, Beckett C, Castle J, et al. (2010) III. Deprivation-specific psychological patterns. Monogr Soc Res Child Dev 75: 48-78.
- 229. Kumsta R, Sonuga-Barke E, Rutter M (2012) Adolescent callous-unemotional traits and conduct disorder in adoptees exposed to severe early deprivation. Br J Psychiatry 200: 197-201.
- 230. Kreppner JM, Rutter M, Beckett C, Castle J, Colvert E, et al. (2007) Normality and impairment following profound early institutional deprivation: a longitudinal follow-up into early adolescence. Dev Psychol 43: 931-946.
- 231.Kreppner J, Kumsta R, Rutter M, Beckett C, Castle J, et al. (2010) IV. Developmental course of deprivation-specific psychological patterns: early manifestations, persistence to age 15, and clinical features. Monogr Soc Res Child Dev 75: 79-101.
- 232. Rutter M, Kreppner J, Sonuga-Barke E (2009) Emanuel Miller Lecture: Attachment insecurity, disinhibited attachment, and attachment disorders: where do research findings leave the concepts? J Child Psychol Psychiatry 50: 529-543.
- 233. Alexander N, Osinsky R, Schmitz A, Mueller E, Kuepper Y, et al. (2010) The BDNF Val66Met polymorphism affects HPA-axis reactivity to acute stress. Psychoneuroendocrinology 35: 949-953.
- 234. Frustaci A, Pozzi G, Gianfagna F, Manzoli L, Boccia S (2008) Meta-analysis of the brain-derived neurotrophic factor gene (BDNF) Val66Met polymorphism in anxiety disorders and anxiety-related personality traits. Neuropsychobiology 58: 163-170.
- Goodyer IM, Croudace T, Dudbridge F, Ban M, Herbert J (2010) Polymorphisms in BDNF (Val66Met) and 5-HTTLPR, morning cortisol and subsequent depression in at-risk adolescents. Br J Psychiatry 197: 365-371.
- 236.Mata J, Thompson RJ, Gotlib IH (2010) BDNF genotype moderates the relation between physical activity and depressive symptoms. Health Psychol 29: 130-133.
- 237.Drury SS, Gleason MM, Theall KP, Smyke AT, Nelson CA, et al. (2011)

Page 15 of 15

Genetic sensitivity to the caregiving context: The influence of 5httlpr and BDNF val66met on indiscriminate social behavior. Physiol Behav.

- 238. Carver CS, Johnson SL, Joormann J, Lemoult J, Cuccaro ML (2011) Childhood adversity interacts separately with 5-HTTLPR and BDNF to predict lifetime depression diagnosis. J Affect Disord 132: 89-93.
- 239. Kegel CAT, Bus AG, van IJzendoorn MH (2011) Differential susceptibility in early literacy instruction through computer games: the role of the dopamine D4 receptor gene (DRD4). Mind, Brain, and Education 5: 71-78.
- 240. Reynolds JN, Weinberg J, Clarren S, Beaulieu C, Rasmussen C, et al. (2011) Fetal alcohol spectrum disorders: gene-environment interactions, predictive biomarkers, and the relationship between structural alterations in the brain and functional outcomes. Semin Pediatr Neurol 18: 49-55.
- 241.Turecki G, Ernst C, Jollant F, Labonté B, Mechawar N (2012) The neurodevelopmental origins of suicidal behavior. Trends Neurosci 35: 14-23.
- 242. Ponce G, Pérez-González R, Aragüés M, Palomo T, Rodríguez-Jiménez R, et al. (2009) The ANKK1 kinase gene and psychiatric disorders. Neurotox Res 16: 50-59.
- 243. Hoenicka J, Garrido E, Martínez I, Ponce G, Aragüés M, et al. (2010) Genderspecific COMT Val158Met polymorphism association in Spanish schizophrenic patients. Am J Med Genet B Neuropsychiatr Genet 153B: 79-85.
- 244. Lesch KP, Selch S, Renner TJ, Jacob C, Nguyen TT, et al. (2011) Genomewide copy number variation analysis in attention-deficit/hyperactivity disorder: association with neuropeptide Y gene dosage in an extended pedigree. Mol Psychiatry 16: 491-503.

Submit your next manuscript and get advantages of OMICS Group submissions

Unique features:

- User friendly/feasible website-translation of your paper to 50 world's leading languages
 Audio Version of published paper
- Digital articles to share and explore

Special features:

•

- 200 Open Access Journals
- 15,000 editorial team
- 21 days rapid review process
- Quality and quick editorial, review and publication processing
- Indexing at PubMed (partial), Scopus, DOAJ, EBSCO, Index Copernicus and Google Scholar etc
 Sharing Option: Social Networking Enabled
- Authors, Reviewers and Editors rewarded with online Scientific Credits
- Better discount for your subsequent articles
- Submit your manuscript at: http://www.editorialmanager.com/omicsgroup/