

Epigenetics in Developmental Disorder: ADHD and Endophenotypes

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Abstract

Heterogeneity in attention-deficit/hyperactivity disorder (ADHD), with complex interactive operations of genetic and environmental factors, is expressed in a variety of disorder manifestations: severity, co-morbidities of symptoms, and the effects of genes on phenotypes. Neurodevelopmental influences of genomic imprinting have set the stage for the structural-physiological variations that modulate the cognitive, affective, and pathophysiological domains of ADHD. The relative contributions of genetic and environmental factors provide rapidly proliferating insights into the developmental trajectory of the condition, both structurally and functionally. Parent-of-origin effects seem to support the notion that genetic risks for disease process debut often interact with the social environment, i.e., the parental environment in infants and young children. The notion of *endophenotypes*, markers of an underlying liability to the disorder, may facilitate detection of genetic risks relative to a complex clinical disorder. Simple genetic association has proven insufficient to explain the spectrum of ADHD. At a primary level of analysis, the consideration of epigenetic regulation of brain signalling mechanisms, dopamine, serotonin, and noradrenaline is examined. Neurotrophic factors that participate in the neurogenesis, survival, and functional maintenance of brain systems, are involved in neuroplasticity alterations underlying brain disorders, and are implicated in the genetic predisposition to ADHD, but not obviously, nor in a simple or straightforward fashion. In the context of intervention, genetic linkage studies of ADHD pharmacological intervention have demonstrated that associations have fitted the “drug response phenotype,” rather than the disorder diagnosis. Despite conflicting evidence for the existence, or not, of genetic associations between disorder diagnosis and genes regulating the structure and function of neurotransmitters and brain-derived neurotrophic factor (BDNF), associations between symptoms-profiles endophenotypes and single nucleotide polymorphisms appear reassuring.

Keywords: Epigenetic; Regulation; Domain; Parent-of-origin; Dopamine; Serotonin; Noradrenaline; Brain-derived neurotrophic factor; Intervention; Endophenotypes

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is distinguished by several highly heterogeneous aspects. It is caused by a multitude of interactive neurobiological and environmental factors operating in a highly complex manner. The consequences of multiple gene interactions with environment and each other through complex mechanisms, such as genetic heterogeneity or polygenicity, with phenotypic variability has contributed to marked individual differences in the manifestation, severity and comorbidity of symptoms in neuropsychiatric and developmental disorders [1-3]. Genetic heterogeneity, allelic or locus, is a phenomenon through which a single phenotype or genetic disorder may be caused by any one of many alleles or non-allele mutations, independently, in contrast to pleiotropy whereby a single gene may cause multiple phenotypic expressions or disorders [4]. Polygenicity refers to the effect by which different genes contribute to a phenotype in concerted action with no main gene effect, or the affect of many genes upon a trait, e.g., the concerted actions of genes in drug sensitization, withdrawal, drug metabolism, and co-morbidity [5-6]. Bilateral inheritance in the “hyperactive child syndrome” was presented as evidence of polygenicity almost four decades ago [7]. The vast heterogeneity in ADHD, with consequential complex etiology, is expressed in a variety of genetic, functional, and biomarker domains. Clinical heterogeneity is a consequence of frequent associations with different co-morbidities and dysregulations in psychosocial and operational functioning. Gene-environment interactions, the basis of epigenetics, may modify the expression of individuals’ genetic background by either strengthening or weakening the effects of genes on phenotypes [8] with particular relevance in psychopathology

[8]. Pennington et al. [9] reviewed evidence for gene-environment interactions, in opposite directions, in ADHD and reading disability (diathesis stress in the former and bioecological in the latter). Epigenetic mechanisms that contribute to several neuropsychiatric disorders [10] and previously considered stable and irreversible conditions, have been shown to be dynamic and may be reversible, even in fully differentiated brain cells [11-13].

Steinhausen [14] has reviewed certain aspects of the disorder pertaining to: (a) selected etiological domains that involve the influences of genes, brain regions, and functions in the interactions of causal factors, and (b) the clinical heterogeneity encompassed in co-morbidity, gender effects, and intervention-outcome. In view of the interaction of genotype with psychosocial factors, the identifications of environmental mechanisms and gene combinations is limited by paucity of candidate environments and gene markers as yet to be studied [15]. Wong et al. [16] measured quantitatively DNA methylation across the promoter regions of the dopamine receptor 4 gene (DRD4), the serotonin transporter gene (SLC6A4/SERT), and the X-linked monoamine oxidase A gene (MAOA) through application of

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DNA sampled in 46 MZ twin-pairs and 45 DZ twin-pairs (total n=182) at the ages of 5 and 10 years. The data suggested that DNA methylation differences are apparent already in early childhood, even between genetically identical individuals, and that individual differences in methylation are not stable over time. This longitudinal-developmental study suggested that environmental influences are important factors accounting for inter-individual DNA methylation differences, and that these influences differ across the genome [but see also 17].

Epigenetics, inherited changes in phenotype or gene expression caused by mechanisms other than changes in the underlying DNA sequence (involving modifications of the activation of certain genes, but not the basic structure of DNA), is implicated in developmental origins of chronic noncommunicable disease [18,19]. 5-methyl cytosine with its role in controlling gene expression and the pattern of methylation is supported by much data that methylation is strongly associated with gene silencing in a variety of biological contexts, the role of chromatin and histone modifications, and the influence of regulatory RNAs [20,21]. Epigenetic regulation may be mediated by DNA methylation, physical changes to chromatin structure, and the action of siRNA molecules (cf. [22]). Between the stage of the embryo and adulthood, several developmental spurts occur in the brain during which activity and proper nutrition facilitate full brain capacity for synaptogenesis and neurogenesis. Malnutrition and adversity underlie the 'gene-switching' over lifetime: gene-switches are positive with adequate social bonding and good nutrients, but negative with shock/trauma, stress, or poor nutrition [23]. Marked neurodevelopmental influences of genomic imprinting set the stage for structural-physiological variation that affect cognition, emotion, and pathophysiology of ADHD (e.g., [24]). Nevertheless, although innumerable gene association studies have provided a huge amount of evidence for multi-involvement for neurotransmitters and metabolic enzymes (e.g., monoamine oxidase [MAO] or tryptophan hydroxylase [TPH]) in genetic predispositions for the disorder, the conflicting results, due to failure to obtain association, are rife [25-27].

Environmental Influences

The contributions of adverse environmental insults to potential risk for childhood and life-cycle disorders have been shown to be widespread [28-32]. The time of introduction of insult, e.g., prenatal, is of particular importance [33-35]. Adversity during periodic catastrophes caused by war and/or disease also has offered a recurrent environmental malefactor [36]. Both prenatal and postnatal stress may exert adverse effects on the brain development that are expressed in cognitive, motor, and emotional domains during childhood, adolescence, and adulthood [37-39]. For example, prenatal maternal stress induced alterations in the behavior of their offspring through elevated levels of corticotrophin-releasing hormones and consequent disruptions in the normal functioning of the hypothalamic-pituitary-adrenal axis [40,41]. It should be noted that the HPA axis alterations are implicated in a variety of postnatal disorders involving the actions of adrenal glucocorticoids [42,43]. Intrauterine growth retardation (IUGR) can reset permanently the HPA axis [44,45], the reprogramming of which may involve persistently altered expression of the hippocampal glucocorticoid receptor (hpGR); dysregulation at this site is linked to increased axis reactivity (cf. [46]). Environmental exposure to a wide variety of agents, characteristically disruptive, has been found to invoke epigenetic processes that affect the developmental trajectories in a generally detrimental manner [48-53]. The epigenetic state of an organism (or "epigenome") incorporates a landscape of complex and plastic molecular events that may underlie the missing link that

integrates genotype with phenotype [54]. Through DNA methylation, histone modifications, and small regulatory RNAs, the epigenome systematically controls gene expression during development, both *in utero* and throughout life. Animal model studies have demonstrated that induction and stability of induced changes in the phenotype of the offspring involve altered epigenetic regulation by DNA methylation and covalent modifications of histones. In turn, opportunities arise for the induction of differential risk of non-communicable diseases in humans by variation in the quality of the early life environment. Burdge and Lillycrop [55] have shown that such epigenetic changes are highly gene specific and function at the level of individual CpG dinucleotides. This was seen through interventions applying the supplementation with folic acid or methyl donors during pregnancy, or folic acid after weaning, which alter the phenotype and epigenotype induced by maternal dietary constraint during gestation. CpG sites are regions of DNA where a cytosine nucleotide occurs next to a guanine nucleotide in the linear base sequence along its length. CpG is shorthand for "—C—phosphate—G—", that is, cytosine and guanine separated by a phosphate, which links the two nucleosides together in DNA. The "CpG" notation is used to distinguish this linear sequence from the CG base-pairing of cytosine and guanine (e.g., [56]). Through epigenetics the methylation of the cytosine within a gene can turn the gene off. Burdge and Lillycrop [55] describe the mechanism that underlies the early life origins of disease and to place these studies in a broader life-course context (see also [57,58]).

Metastable epialleles, sensitive to environmental influences such as diet, undergo molecular changes that, once established, remain for the life of the individual [59]. These modifications are epigenetic, and in some cases they may survive across generations, that is, through meiosis. This is termed transgenerational epigenetic inheritance. Metastable epiallele genes are variably expressed in genetically identical individuals due to epigenetic modifications established during early development [60]. Maternal nutrition and environment have been shown to affect metastable epiallele methylation patterns and subsequent adult phenotype. Dolinoy et al. [61] observed variable histone patterns in the 5' long terminal repeat (LTR) of the murine viable yellow Agouti (A(vy)) metastable epiallele. The observed region contains 6 CpG sites, which are variably methylated in isogenic A(vy/a) offspring. Yellow mice, which are hypomethylated at the A(vy) LTR and exhibit constitutive ectopic expression of agouti (a), displayed also enrichment of H3 and H4 di-acetylation. Pseudoagouti mice, in which A(vy) hypermethylation, considered to silence ectopic expression, displayed enrichment of H4K20 tri-methylation. Bernal and Jirtle [62] found that using the Agouti viable yellow (A(vy)) mouse model, dietary BPA exposure was shown to hypomethylate both the A(vy) and the Cabp(IAP) metastable epialleles. This hypomethylation effect was counteracted with dietary supplementation of methyl donors or genistein. Epigenomes present reactive systems with lability allowing reception and response to environmental perturbations, thereby ensuring survival during fetal growth. Adverse environments may impose through genotoxic and epigenotoxic effects on the population gene-pooled genome. This type of genetic pliability may lead to aberrant epigenetic modifications that persist into later life and induce numerous disease states. They suggest that epigenotoxicity could lead to numerous developmental, metabolic, and behavioral disorders in exposed populations, whereby the heritable nature of epigenetic changes also increases the risk for transgenerational inheritance of phenotypes [62]. Bell et al. [63] have examined genotype-epigenotype interactions in the context of Type 2 Diabetes (T2D), focussing on known regions of genomic susceptibility. They identified increased

DNA methylation on the FTO obesity susceptibility haplotype, tagged by the rs8050136 risk allele A ($p = 9.40 \times 10^{-4}$, permutation $p = 1.0 \times 10^{-3}$). Sequence level analysis, followed by pyrosequencing validation, revealed that the methylation difference was driven by the co-ordinated phase of CpG-creating single nucleotide polymorphisms (SNPs) across the risk haplotype. This 7.7 kb region of haplotype-specific methylation, encapsulates a “highly conserved non-coding element,” previously validated as a long-range enhancer, and supported by the histone H3K4me1 enhancer signature. Taken together, these results displayed the integration of genome-wide association SNP and epigenomic DNA methylation data can identify potential novel genotype-epigenotype interactions within disease-associated loci. In short, environmental influences may be adverse (above) or benign (e.g. the role of physical exercise) in discussing the epigenetics of a developmental disorder, such as ADHD, an attempt is made to seek associations between adverse environments and genetic configurations with endophenotypes (disorder symptoms) rather than the diagnosis itself.

Epigenetics in ADHD

In the etiopathogenesis of ADHD, environmental insults that contribute to adverse risk factors have been documented amply [64-67]. Incidence analyses, including meta-analysis studies, have indicated that the world-wide prevalence of ADHD may well be in excess of 5% [68-70], with astronomical social and economic costs [71]. Gustafsson and Källén [72] reported that the results of a multiple logistic regression analysis indicated that ADHD was significantly associated with several environmental factors: a young maternal age, maternal smoking, maternal birthplace in Sweden, and preterm birth <weeks, as well as a male predominance. Wallis et al. [73] have reviewed several notions that are required for sufficient consideration of ADHD genetics, these included: (a) the complexities involved, (b) evidence for a primarily genetic component, (c) evidence that there exist only a few genes with major effects, (d) identification of the best candidate genes, and (e) descriptions of gene-environment interactions, or the essential basis of epigenetics. As the specificity (or lack of) of genes, phenotypic effects and risk factors unfolds, it will be observed that these notions both verified and contradicted. However, chromosomal regions containing potential ADHD predisposing loci, some overlapping in two or more studies, including 5p, 6q, 7p, 11q, 12q, and 17p, have been identified through family-based linkage studies (cf. [74]). Confirmed association of ADHD with several candidate genes, e.g., DAT1, DRD4, SNAP5, 5HTT, HTR1B, and DBH, was reported several years ago [75], but also see [74]. For example, Forero et al. [76] performed a meta-analysis study aimed at eight common variants located in five top candidate genes, all implicated in synaptic transmission and plasticity, for ADHD (brain-derived neurotrophic factor [BDNF], HTR1B, SLC6A2, SLC6A4, and SNAP25). They observed a weak but significant association with a SNP located in the 3' UTR region of the SNAP25 gene (synaptosomal-associated protein 25, rs3746544, T allele). At glutamatergic synapses SNAP-25 decreases the Ca^{2+} responsiveness.

Developmentally, the disorder is characterized by behavior hyperactivity, attentional and concentration problems, and impulsiveness, and there is only a rudimentary understanding of the etiology. Nevertheless, the relative contributions of genetic and environmental factors provide rapidly proliferating insights into the developmental trajectory of the condition, both structurally and functionally [77-79]. Cook et al. [80] described a genetic association between ADHD and the 10 repeat allele of a variable number of tandem repeat (VNTR) polymorphism within the 3'-untranslated region of

the dopamine transporter gene (DAT1: SLC6A3). Epigenetic factors provide a myriad of possibilities for disorder susceptibility concerning a broad spectrum of neuropsychiatric conditions, including ADHD [38,81,82]. Mill and Petronis [83] have described the associations between early developmental insults and ADHD that arise from epigenetic dysregulations. They proposed that the elucidation of the processes linking specific environmental pathogens to the eventual expressions of the disorder will uncover avenues for preventative and therapeutic intervention [84]. Das et al. [85] have studied the interaction between ten functional polymorphisms in DRD4, DAT1, MAOA, COMT, and DBH genes were explored in the Indo-Caucasoid population. Case-control analysis revealed higher occurrence of DAT1 intron 8 VNTR 5R allele in cases; significant preferential transmission of the 7R-T (DRD4 exon3 VNTR-rs1800955) and 3R-T (MAOA-u VNTR-rs6323) haplotypes were obtained from parents to probands. Gene-gene interaction analysis revealed significant additive effect of DBH rs1108580 and DRD4 rs1800955 with significant main effects of DRD4 exon3 VNTR, DAT1 3'UTR and intron 8 VNTR, MAOA u-VNTR, rs6323, COMT rs4680, rs362204, DBH rs1611115 and rs1108580, thereby pointing towards a strong association of these markers with ADHD. Correlation between gene variants, high ADHD score, and low DBH enzymatic activity was noticed also, especially in male probands.

Association studies in ADHD offer conflicting data [86-91]. Kebir et al. [92] identified 29 studies that examined 10 genes (DRD4, DAT1, COMT, DBH, MAOA, DRD5, ADRA2A, GRIN2A, BDNF, TPH2) in relation to neuropsychological traits (endophenotypes) that were relevant for ADHD, in this case with difficulties involving Continuous Performance Test variables. Their most consistent result involved the association of high reaction time variability with the 7-repeat allele absence specific to ADHD, and the 10-repeat homozygosity. The authors outlined several methodological issues and confounding factors that have bedevilled reliable conclusions. These included measurement errors, developmental alterations in cognitive abilities, gender, psychostimulant effects, and the presence of co-morbid conditions. Nevertheless, Brookes et al. [93,94] have shown association between ADHD and allele 6 of a VNTR mapped to intron 8, DNA region within a gene that is not translated into protein, of DAT1. Non-coding intron sections are transcribed to precursor mRNA (pre-mRNA) and some other RNAs (such as long noncoding RNAs), and subsequently removed by a process called splicing during the processing to mature RNA. After intron splicing (i.e., removal), the mRNA consists only of exon derived sequences, which are translated into a protein [95]. Other studies have presented more-or-less confirmatory results [96,97].

Parent-of-Origin Effects

In the light of family, adoption, and twin studies, it is apparent that a number of genetic mechanisms are implicated, one of which is *genomic imprinting*. The transmission of abnormalities has been shown to be dependent upon the sex of the parent from whom they are inherited. Genomic imprinting may occur by one parent “marking” a gene by DNA methylation, through addition of a carbon (methyl group) to the DNA base, to indicate how their gene is to be used. Parent-of-origin effect offers a general notion that describes two distinctive phenomena: parent-of-origin effects on *transcription* and parent-of-origin effects on *mutation rates*. A parent-of-origin effect on transcription, or genomic imprinting, results from epigenetic modification of the genome which, in turn, results in unequal transcription of parental alleles [98]. In imprinted genes, one allele is silenced according to its parental origin, and imprinted traits are, in turn, passed down the maternal or paternal

line [99]. In a study of parent-of-origin effects in ADHD, Goos et al. [100] investigated 60 children with maternal-only history of ADHD and 131 children with paternal-only history of ADHD. The children were compared on three domains for which prior evidence suggested parent-of-origin effects might exist: core symptoms, disruptive behavior, and depression. It was shown that the maternal history group received higher ratings of behavior disorder (ADHD, conduct disorder [CD], and oppositional symptoms) than the paternal history group. They observed also parent-of-origin effects for depression, with the paternal-only history group rating themselves as significantly more depressed than children in the maternal-only history group, in particular the girls. According to their account, elevated paternal transmission, relative to maternal, implied genomic imprinting, and the interaction with proband sex indicated the involvement of the sex chromosomes or sex-specific physiological or hormonal factors. There is accumulating support for the notion that genetic risks for neuropsychiatric disorders often interact with the social environment, the parental environment in infants and young children. In order to increase understanding of gene-environment interactions involving early parenting, Lahey et al. [101] tested interactions between maternal parenting and the VNTR polymorphism in the 3' untranslated region of the dopamine transporter gene of children. A 9-year longitudinal study of 4-6-year-old children meeting criteria for ADHD and demographically matched controls was carried out. The researchers obtained a significant inverse relation between levels of both positive and negative parenting at 4-6 years and the number of later symptoms of CD, but mainly among children with two copies of the 9-repeat allele of the VNTR.

Parent-of-origin effects and risk for ADHD have been investigated with much attention to detail, cf. [102], although here too evidence is conflicting [103-106]. Hawi et al. [107] examined the parent-of-origin effect at DAT1 (paternal over transmission of ADHD-associated alleles) in three independent samples consisting of Irish Sample 1 (178 ADHD nuclear families), Irish Sample 2 (52 trios in a sample of 108 nuclear families of children with ADHD), and English Sample (63 parent-proband trios and 44 mother-child duos), providing a total of 1248 ADHD nuclear families. They have reported paternal over-transmission of risk alleles in some ADHD-associated genes. An IMAGE sample provided strong support for a parent-of-origin effect for allele 6 and the10 repeat allele (intron 8 and 3'UTR VNTR, respectively). Their findings thereby lend support for the phenomenon of paternal over-transmission of the DAT risk alleles. Hawi et al. [104] reported a systematic over-transmission of paternal alleles at candidate genes associated with ADHD. For the nine genes included in their analysis, the overall odds ratio for paternal transmission was 2, compared with 1.3 for maternal transmission (paternal vs. maternal $\chi^2=9.6$; $p=.0019$). It was concluded that transmission to female participants from either parent, was significantly stronger than to males. Notwithstanding, the paternal over-transmission effect has been documented [97,108].

The notion of endophenotypes that are markers of an underlying liability to psychiatric disorders may facilitate detection of genetic risks relative to a complex clinical disorder, such as ADHD [109-111], and motor response inhibition offers a prime candidate endophenotype in ADHD. Certain behavioral symptoms can be characterized as stable phenotypes with a clear genetic connection: inheritable, state-dependent disorders whereby endophenotype and illness co-segregate within families. For example, siblings of ADHD probands, while not behaviorally expressing the disorder, present ADHD-associated deficits in response inhibition [112,113]. Goos et al. [114] studied covariation in inhibitory control and differential covariation as a

function of parental sex in children with ADHD, unaffected siblings, and their biological parents by applying several validity criteria for inhibitory control as an endophenotype, including sensitivity to the disorder and presence in unaffected relatives. They obtained inhibitory control deficits in children with ADHD as well as in their parents, independent of symptom severity in both generations: inhibitory control ability in children was significantly predicted by the ability of their parents, particularly their fathers. They concluded that inhibitory control deficit is a cognitive marker of genetic risk shared by parents and offspring and that endophenotype notion pertains to differential parental contributions to this risk. This observation is consistent with findings of parent-of-origin effects in the transmission of certain risk alleles observed in molecular analyses [115]. Wood and Neale [116] described the utility of twin studies as an important research tool in the development of endophenotypes, defined as alternative, more highly heritable traits that act at earlier stages of the pathway from genes to behavior.

Hill et al. [117] indicated that the intron 8 VNTR is a functional variant with an ADHD susceptibility allele having reduced activity (see also [93,118,119]). Jooper et al. [120] presented findings that support a role for the DAT gene 3'-UTR VNTR polymorphism in modulating the response of some behavioral dimensions to methylphenidate in children with ADHD. Further, investigating $G_{\alpha_{olf}}$ gene GNAL involvement in ADHD, Laurin et al. [121] studied the inheritance pattern of 12 GNAL polymorphisms in 258 nuclear families ascertained through a proband with ADHD (involving 311 affected children). The $G_{\alpha_{olf}}$ -like subunit $G_{\alpha_{olf}}$ is expressed in D_1 -rich brain regions involving D_1 and D_5 receptor mediation of adenylyl cyclase activation. Their categorical analysis of individual marker alleles demonstrated biased transmission of one polymorphism in GNAL intron 3 (rs2161961) that was associated with inattention and hyperactivity/impulsivity. They found also a strong maternal effect with preferential transmission of maternal alleles for rs2161961A and rs8098539A.

Neurotransmitters

Dopamine-Regulating Genes in ADHD: Early adverse stress trauma environments are implicated in ADHD over national boundaries [122-124]. Deprivation in social and environmental conditions may perturb early cellular patterns of neurodevelopment that are manifested as disorder expression in later life [125], with aspects of ADHD originating in early deprivation [126,127]. Epigenetic factors have implicated both dopamine and serotonin in ADHD symptoms, particularly impulsive behaviors. For example, functional gene variants in the serotonin transporter gene-linked polymorphic region 5-HTTLPR are implicated in neural mechanisms of disorders relating to impulsive control [128,129]. Moreover, candidate gene studies in ADHD children have had a predominating focus upon the monoaminergic neurotransmitter systems with particular attention on dopamine and the major focus upon DAT1 and the DRDs dopamine receptor genes. Early institutional deprivation with ADHD as outcome [130] was shown to vary greatly over individuals despite high levels of adversity [131]. Perinatal environmental risk is moderated by genetic factors in determining outcome [132,133]. The DAT1 (SLC6A3) transport and DRD4 receptor genes are implicated in the pathophysiology of ADHD [83,134,135]. Stevens et al. [136] examined the moderating effect of DRD4 and DAT1 functional polymorphisms on deprivational influences following institutionalization upon ADHD in a longitudinal study with participants at ages 6, 11, and 15 years-of-age. This type of study would ensure both a proper establishment of a G x E hypothesis, and a test of developmental G x E mechanisms.

The investigators observed that the early institutional-deprivation as an ADHD risk factor was moderated by the DAT1 but not the DRD4 genotype. These effects appeared first in early-adolescence and persisted to mild-adolescence, which was their ultimate period of analysis. The authors concluded that the results: (a) provided evidence for developmental continuities in the G x E interaction, (b) explained part of the heterogeneity in ADHD outcomes following institutional deprivation, and (c) further contribute to understanding of environmental determinants of ADHD in the institutional setting. In a broader perspective, their findings provide an essential description of the developmental trajectories to be defined in developmental disorder.

Following the initial report by Comings et al. [137] of Taq A1 allele association in ADHD individuals, and as Blum et al. [74] have reviewed, both positive and negative findings related to the putative association of DRD2 A1 allele as a critical gene polymorphic link to ADHD and related behaviors are documented (see also [138,139]). Plausible evidence for the ADHD association is derived from a number of studies. For example, Sery et al. [140] obtained statistically different genotypic and allelic frequencies of DRD2 polymorphism between the two groups of boys that they studied. Similarly, Kopeckova et al. [88] observed that ADHD-risk (a) was linked to a risk allele in DRD2 gene, the 5-HTT gene, and the DAT1 gene, (b) was elevated at homozygotes for risk alleles in the same genes and for polymorphisms G444A and C1603T in dopamine- β -hydroxylase (DBH), and (c) was increased in the presence of allele DBH +444A and allele DBH +1603T. More recently, Paclt et al. [141] studied a sample of 269 ADHD boys and a control group of 317 boys. Comparison of genotype frequencies indicated a highly significant difference between the two groups, with the A1 allele having a 4.359-fold higher risk for ADHD. Within the context of association studies focused upon endophenotype, Esposito-Smythers et al. [142] found interaction effects between the DRD2 TaqIA polymorphism and CD, also between A1+ status and impulsiveness, whereby adolescent carriers of the A1 allele with CD or impulsiveness, reported higher levels of problematic alcohol use than non-carriers (A2/A2 or A1-). They obtained the same interaction effect between impulsiveness and DRD2 TaqIA polymorphism regarding severity of problem drug use. However, no interaction effects were obtained between the DRD2 allele status and ADHD on severity of problem drinking or drug use. Blum et al. [74] discussed the viability of ADHD genetic testing at birth with obvious diagnostic benefits probable via: (a) coupling of genotyping with psychometric instruments, (b) that dopaminergic genotyping to determine high risk future substance abuse may affect use in adolescents, and (c) applications of D2 agonists for ADHD symptoms related to specific candidate polymorphisms. Following several independent meta-analyses confirming the association of DRD2 polymorphisms with impulsive-addictive-compulsive behaviors that include ADHD symptoms, Blum et al. [143,144] coined the notion of "Reward Deficiency Syndrome" implicating dopamine D2 gene variants (see also [145-147]).

It is known that an adverse prenatal environment, e.g., intrauterine growth retardation (IUGR), elevates the risk for negative neurobehavioral developmental outcomes, affecting for example approximately 10% of all US infants, a known risk factor for ADHD [148,149]. Nutritional deprivation offers another disease sharing pathophysiological expressions with the disorder particularly with respect to impulsiveness [150]. In a mouse model of ADHD, Vucetic et al. [151] fed mouse dams on a protein deficient (8.5% protein) or isocaloric control (18% protein) diet through pregnancy and lactation (a well validated rodent model of IUGR), and then studied dopamine-related gene expression, dopamine content, and behavior

in adult offspring. IUGR offspring displayed a six to eightfold over-expression of dopamine-related genes (tyrosine hydroxylase and dopamine transporter) in brain regions related to reward processing, i.e., ventral tegmental area, nucleus accumbens, prefrontal cortex, and hypothalamus, as well as increased number of TH-ir neurons in the ventral tegmental area and increased dopamine in the prefrontal cortex. It was found too that methylation of the promoter region of Cyclin-dependent kinase inhibitor 1C, critical for dopaminergic neuron development, was decreased by half and there was a resultant two to sevenfold increase in its expression across brain regions. Prenatal dietary-restricted animals showed endophenotypes similar to ADHD symptoms.

Variations in the catechol-O-methyltransferase (COMT) gene, which encodes for the enzyme, affect functioning in the prefrontal region more markedly than other regions. The COMT genotype has been shown to influence prefrontal dopaminergic activity cognitive expressions in children and adolescents [152,153]. The COMT gene has been associated with phenotypic variation among ADHD children with the Val/Val homozygote presenting symptoms of conduct disorders, aggressivity, and criminal acts [154]. Nobile et al. [155] studied the association of the functional Val158Met COMT polymorphism and socioeconomic status with CD, oppositional defiant disorder (ODD), and ADHD in a general population sample of 575 Italian pre-adolescents aged 10 to 14 years. They obtained a significant COMT x Socioeconomic Status interaction with ADHD problems and higher scores among children with Val/Val COMT genotype and low socioeconomic status. There was a significant association of socioeconomic status, ADHD, and CD problems. Thus, socioeconomic status appears to offer a notable environmental factor. In a study of gene-environment interaction effects on autism spectrum symptoms in ADHD children (aged 5 to 17 years), Nijmeijer et al. [156] found that the COMT Val/Val genotype interacted with maternal smoking during pregnancy by elevating stereotypy.

Discordant DNA methylation patterns in adolescent or adult MZ twin pairs have shown that the epigenome is in constant drift over the life course in response to stochastic and environmental factors, but in infancy the situation appears 'prehensile'. Several features of neuropsychiatric disorders, such as ADHD, are consistent with an epigenetic dysregulation, including discordance of monozygotic twins, late age of onset, parent-of-origin and gender effects, and fluctuating disease course have permitted insights regarding the epigenome and its role in maintenance of normal genomic functions, as well as disease etiopathogenesis [157]. Ilott et al. [158] have reported heritability and genetic association between specific risk alleles and ADHD symptom expressions in a population of 2-year-old twins showing modest evidence for DAT1 and NET1. In order to ascertain extent of additive genetic variance influence on symptoms, Ilott et al. [158] studied 312 pairs at age-points, 2 and 3 years. It was found that at these age-points ADHD symptoms were highly heritable ($H^2 = 0.79$ and 0.78 , respectively) but with significant level of genetic change from the 1st to the 2nd age-point, modest non-shared environmental influence. They obtained also association signals in DAT1 and NET1, with specific effects of 5-HTT and DRD4 at three-years-of-age (see also [158,159]).

Several studies have focussed on dopamine and serotonin candidate genes' association with impulse control. Ha et al. [160] evaluated the influence of 5-HTTLPR and dopamine receptor D4 (DRD4) polymorphisms and their interaction with performance on the Iowa Gambling Task (IGT) in 159 genotyped subjects. After controlling for gender, age, and impulsiveness, they observed no main

effects of 5-HTTLPR and DRD4 gene polymorphisms on total IGT score. Nevertheless, there was a significant effect on the interaction between 5-HTTLPR and DRD4 on total IGT score. In the presence of the 5-HTTLPR S'S' (SS+SL(G)+L(G)L(G)), subjects with the DRD4 2R+ (2 repeat carrier) had higher total IGT scores compared to those with the DRD4 2R-. In contrast, in the absence of the 5-HTTLPR S'S', subjects with the DRD4 2R- had a higher total IGT score than those with the DRD4 2R+. Following division of IGT scores into the first and second half of the trials, the 5-HTTLPR by DRD4 interaction effects were stronger in the second half block (decision under risk) than in the first half block (decision under ambiguity). The authors concluded that the DRD4 genotypes might influence decision-making performance differently according to the background genotypes of 5-HTTLPR thereby modulating the expression of impulsivity in decision-making. However, there are studies that have failed to obtain associations with the disorder. Mick et al. [161] failed to identify an association with the val66 allele in BDNF, the COMT-I allele, or the HTTLPR short allele.

Serotonin-Regulating Genes in ADHD: The serotonergic system is critically involved in physiological functions [162], neuropsychiatric disorders [163,164], and regulation of cognitive-emotional functioning [165,166] unsurprisingly, serotonin genes have been strongly associated with cognitive-emotional profiles burdened by impulsiveness. For example, Szily et al. [166] showed that the s-allele of the serotonin transporter gene is associated with a vulnerable cognitive style related to the appraisal of negative emotions. The association of serotonin-influencing genes with impulsivity symptoms of ADHD has received some support [167-172], but yet several investigations have failed to obtain any links [173-175]. Impulsiveness, a heterogenous endophenotype [176] and cardinal symptom of ADHD [177], is expressed in a multitude of neuropsychiatric disorders and comorbidities [178-182]. The serotonin HTR1A gene is located on the long arm of chromosome 5 (6q11.2-13) with the functional C(-1019)G polymorphism (rs6295) a common SNP in the promoter region of the gene [183]. The C(-1019)G functional polymorphism (rs6295) has been suggested to regulate the 5-HT(1A) receptor gene (HTR(1A)) expression in presynaptic raphe neurons, namely, increased receptor concentration and reduced neuronal firing could be associated with the G allele [184]. However, although the putative association between C(-1019)G functional polymorphism and personality traits such as neuroticism and harm avoidance, linked with impulsivity, was observed in carriers of the G allele compared with carriers of the C allele [185], several studies have failed to do so, or for other expressions of neuropsychiatric emotionality [186-188]. Despite this, Benko et al. [189] studied the relationship between HTR1A C(-1019)G polymorphism and impulsiveness in 725 healthy volunteers. They obtained significant differences between the C(-1019)G genotype groups (GG vs. GC vs. CC) whereby subjects carrying the GG genotype expressed more impulsiveness than GC or CC carriers.

The uncertain nature of the link between ADHD and serotonin polymorphisms may be illustrated: Li et al. [190] studied the association between adolescent behavior outcome in ADHD and serotonin pathway genes, including the -1438A>G polymorphism of the serotonin 2A receptor gene (HTR2A) and the -759C>T polymorphism of the serotonin 2C receptor gene (HTR2C). The former, -1438A>G polymorphism, was shown to be related to remission in ADHD, especially functional remission. Similarly, Li et al. [191] found that the T allele of the 83097 C>T polymorphism of HTR4 (serotonin 4 receptor gene) showed a tendency for preferential transmission to probands with ADHD, and that the C/G haplotype of the 83097 C>T and 83198 A>G polymorphisms, the C/G/C haplotype

of these and the -36 C>T polymorphism were under-transmitted to probands with ADHD. Contrastingly, Li et al. [192] examined five variants in three serotonin genes (those coding for serotonin receptors 2A (HTR2A), 5A (HTR5A) and 6 (HTR6)) in a relatively large sample of ADHD nuclear families. Their results did not support any role for these serotonin genes in ADHD. As Kuntsi et al. [193] have argued, it is possible that the real strength of the observed/non-observed associations may be underestimated in certain studies, lacking sufficient consideration of linkage disequilibrium, allelic heterogeneity, population differences, and gene by environment interactions. Ribases et al. [194] analyzed SNPs for 19 serotonin genes from a clinical sample of 451 ADHD patients (188 adults and 263 children) and 400 controls using a population-based association method. They obtained several significant associations: (a) the DDC gene was strongly associated with both adult and childhood ADHD (DOPA decarboxylase (DDC) is an enzyme involved directly in the synthesis of dopamine and serotonin, and indirectly in the synthesis of noradrenaline); (b) the MAO_B gene was found specifically associated in the adult ADHD sample; and (c) the 5HT2A gene showed evidence of association only with the combined ADHD subtype both in adults and in children. Their findings supported the notion of a serotonergic system contribution to the genetic predisposition for ADHD. Additionally, Landaas et al. [195] found a modest association for functional promoter polymorphism, 5-HTTLPR, with 448 adult ADHD patients and 580 controls from Norway. In the context of serotonin and impulsive behavior, Roiser et al. [196] indicated that the less active S allele of the serotonin transporter 5HTTLPR polymorphism was linked to elevated sensitivity to probability for success on a risky-choice task. Possession of this polymorphism induced disadvantageous choice behavior in the Iowa Gambling Task (IGT) due either to lack of persistence or slower acquisition of successful decision-making [197,198]. Failure to learn from faulty decision-making resulting in punishment presents a different aspect of impulse-control impairment; possibly, 5HTTLPR variations modulate sensitivity to punishments, since LL homozygous individuals were less sensitive to punishment-related information [199,200].

Impulsive behavior, broadly "action without foresight" (cf. [176]), may be linked strongly to aggressive acts (impulsive aggression) and variations in serotonin neurotransmission with or without ADHD diagnosis [201-205]. Failure of executive inhibitory functioning is linked to the emotional lability and dysfunctional motor control expressed in impulsive aggressiveness [206-209], often displayed in maladaptive responding and misappropriate actions of ADHD individuals [210-212]. For example, maladaptive and impaired, impulsive decision-making linked to emotional dysregulation, the real/potential endophenotypes, and modulated by serotonergic genotypes associated with suicidal behavior, have presented relevant markers for identification of patients with vulnerability [213]. ADHD children have displayed greater impairment in controlled than automatic response processing and inhibition [214]; these disorder states have been shown to be related to ADHD [215-217] and notably serotonergic functioning in ADHD [218-222]. Using a family-based association test (FBAT-PC), Oades et al. [223] found a genetic influence on both serotonergic and dopaminergic involvement in impulsiveness by ADHD children: Trends for separate and overlapping influences on impulsive-aggressiveness (TPH, HTR1E) and cognitive-impulsiveness (SERT/SLC6A4 variant), with phenylethanolamine N-methyltransferase association, were obtained. Salo et al. [224] studied the interaction between polymorphisms of COMT and serotonin receptor 2A genes in a subsample of 1214 healthy Finnish adult volunteers. They

demonstrated an interaction between COMT Val158Met and HTR2A T102C polymorphisms associated with impulsiveness. T/T carriers of HTR2A T102C polymorphism, that possessed also the Met/Met genotype of COMT Val158Met SNP, scored significantly higher on impulsiveness than the Val allele carriers thereby further emphasising the interactions between dopaminergic and serotonergic genes underlying impulsiveness.

Studies manipulating serotonergic neurotransmission through, e.g., tryptophan availability alterations, further demonstrate a role in decision-making and impulsive behavior [225-228], with tryptophan supplements improving decision-making [229]. Using a rapid, event-related go/no-go task, Rubia et al. [230] found that acute tryptophan depletion significantly reduced right orbito-inferior prefrontal activation during the no-go condition, and increased activation in superior and medial temporal cortices, thereby indicating serotonergic modulation of right inferior prefrontal cortex during inhibitory motor control. Jollant et al. [231] observed that genetic variations in the tryptophan hydroxylase 1 and 2, TPH1, and TPH2 genes and MAOA gene were associated with worse IGT performance in suicide attempters. Variations in the TPH2 gene have been implicated repeatedly in suicidal behavior and neuropsychiatric disorders [232-235]. Juhasz et al. [236] genotyped seven haplotype tagging SNPs in the TPH2 gene, as well as previously reported functional polymorphisms from the other genes (rs1800532, 5HTTLPR, and rs6295), and assessed risk-taking behavior using the IGT. They found that carriers of the more prevalent haplotype evidenced less risk-taking on the tasks applied. In order to examine mechanisms by which serotonergic neurotransmission affects impulsivity, Walderhaug et al. [237] studied the triallelic system of the serotonin transporter gene linked polymorphic region (5-HTTLPR) and acute manipulation of serotonin in 52 healthy participants (38 men and 14 women) receiving acute tryptophan depletion or placebo in a randomized, double-blind, parallel group experiment, using a test of response control. They obtained a dose-dependent effect for the short (S') allele of the 5-HTTLPR upon subjects' impulsive responding, whereby individuals with the S'/S' genotype were more impulsive than individuals with the L/S' genotype, who in turn were more impulsive than the L/L genotype. Acute tryptophan depletion increased impulsiveness in male participants but decreased impulsiveness in female participants.

To investigate epigenetic influences on serotonergic genes, Kinaly et al. [238] developed an experimental Rhesus macaque model of early life stress to test whether or not epigenetic regulation of the 5-HTT may contribute to G x E interactions that influence behavior and emotion. They studied 87 infant monkeys (3-4 months of age) that were either mother reared in large social groups (n=70) or nursery reared (n=17), and during maternal/social separation, the infants' blood was sampled and behavioral stress reactivity recorded, with PBMC DNA and RNA samples were used to determine rh5-HTTLPR genotype. As observed with human subjects, the carriers of the low-expressing rh5-HTTLPR alleles exhibited higher mean 5-HTT CpG methylation, which was associated with lower PBMC 5-HTT expression. Higher 5-HTT CpG methylation, but not rh5-HTTLPR genotype, exacerbated the effects of early life stress on behavioral stress reactivity in infants. As a landmark in epigenetics, Caspi et al. [239] showed the interaction of stressful environment and genetic variation of 5-HTTLPR on suicidality through which individuals with one or two copies of the short (s) allele were more vulnerable to adversity than individuals homozygous for the long (l) allele. In this context, Jacob et al. [240] studied the interactions of serotonergic candidate genes, including 5-HTT, HTR1A and TPH2, with burden of life events in 183 adult patients presenting personality

disorders and 123 presenting adult ADHD. They observed that only the G allele of HTR1A rs6295 increased the risk of emotional-dramatic cluster B personality disorders, and decreased risk of anxious-fearful cluster C. There was nominal evidence of 5-HTTLPR and TPH2 SNP rs4570625 on personality disorder occurrence.

Noradrenaline-Regulating Genes in ADHD: There are several converging lines of evidence implicating dysregulations in noradrenergic functions in the pathophysiology of ADHD [241], and alterations in noradrenaline-influencing genes [242-244]. Nevertheless, as in the cases of both dopamine and serotonin, a number of studies have failed to obtain any association [174,245,246]. Barr et al. [247] tested the gene for the noradrenaline transporter (NET1) as a putative susceptibility factor for ADHD by applying three polymorphisms located in exon 9, intron 9, and intron 13. They examined the inheritance of these polymorphisms in a sample of 122 families with a total of 155 children with ADHD identified through an ADHD proband. They investigated this gene by screening the probands for five known amino acid variants to determine whether or not they contributed to the ADHD phenotype but observed only one (Thr99Ile) in the sample. They indicated that since the frequency of this variant (1.8%) was similar to that previously reported in a control sample (2.2%), it was unlikely that this variant is related to the ADHD phenotype; thus, their results failed to support the NET1 gene as a major genetic susceptibility factor in ADHD. On the other hand, Roman et al. [248] tested for association between the dopamine- β -hydroxylase (DBH) gene and ADHD in a sample of 88 Brazilian nuclear families. The haplotype relative risk (HRR) analysis of the DBH TaqI restriction site polymorphism had shown a preferential transmission of the TaqI A2 allele in their whole ADHD sample. They found that the significant effect of the A2 allele was stronger when only families with no ADHD parental diagnosis were considered, suggesting the contribution of this gene to ADHD susceptibility.

Using preparations of prepared gene expression profiles of *in vitro* differentiating wild type and norepinephrine transporter-deficient (NETKO) mouse neural crest cells with long serial analysis of gene expression (LongSAGE), Hu et al. [249] showed loss of NET function during embryonic development in the mouse deregulates signalling pathways that are critically involved in neural crest formation and noradrenergic cell differentiation. Kollins et al. [250] applied haplotype-tagging SNP analyses in order to identify molecular genetic substrates of quantitative phenotypes derived from performance on a Continuous Performance Task (CPT) in 364 individuals sampled from 152 families, with probands, their affected and unaffected siblings, and parents. The CPT measures sustained and selective attention and impulsivity by requiring individuals to press (or not press) certain keys depending on the stimulus that flashes on a computer screen. The test usually lasts between 14 and 20 minutes and is designed purposely to be repetitive and monotonous. Good performance requires individuals to sustain their attention to a selectively boring task and to refrain from impulsive responding. Errors of omission, i.e., failure to press the designated key in response to the target stimulus flashing, and errors of commission, i.e., key-pressing responses to a non-target stimulus, together with several other variables, e.g., reaction time and reaction time variability, are computed; individuals' scores may be compared then to typical performance by individuals with the same age, gender, etc. In the study by Kollins et al. [250], significant associations were identified between CPT commission errors and SNPs in the DRD2 gene (rs2075654, rs1079596), and between reaction time variability and a SNP in the NET gene (rs3785155). Errors of commission occurred when subjects answered a question incorrectly; a pattern of heightened emotional reactivity and commission errors is typical for individuals

with elevated dissociation scores [251]. On the other hand, Hess et al. [252] carried out association tests with DBH genotypes on four independent samples: healthy volunteers (n=387), patients presenting affective disorders (n=182), adult ADHD patients (n=407), and patients presenting personality disorders (n=637). Their results suggested a dimensional rather than categorical effect of genetic variance in DBH activity, possibly due to the underlying association of the TT genotype at DBH-1021 with impulsive personality traits. Dissociative symptoms have been found to be increased in ADHD individuals [253-256]. Joung et al. [257] performed the genetic association study for a functional -3081(A/T) polymorphism, located in the promoter region of SLC6A2, the norepinephrine transporter gene and a possible candidate gene for ADHD, in a Korean population of 103 male patients with ADHD and 103 normal male controls. Their findings provided further evidence of association between ADHD and -3081(A/T) polymorphism of SLC6A2 (see above).

Neurotrophic Factor-Regulating Genes in ADHD

Neurotrophic factors, participating in the neurodevelopment, survival, and functional maintenance of brain systems, are involved in neuroplasticity alterations underlying brain disorders and are implicated in the genetic predisposition to ADHD [39,258,259]. The BDNF gene, located at 11p13-14, has several SNPs, most common is rs6265, as evidenced by the observation of elevated BDNF serum levels in Met allele carriers [260]. Despite ubiquitous inconsistent findings (e.g., [261,262]), several investigations support the BDNF association involvement in ADHD [263-266] (but see also [267]). Conner et al. [210] found that among NTF3, NTRK2 (TrkB), NTRK3 (TrkC), BDNF, and p75(NTR), none of the SNPs showed significant association with ADHD symptoms, except for one polymorphism within the exon of NTF3 (rs6332) that showed a trend toward an association between the A-allele and increased scores using both the retrospective childhood analysis Wender-Utah Rating Scale and the adult ADHD assessment Wender-Reimherr interview. In order to attempt a consolidation of inconsistencies among case-control and family-based associations pertaining to p.Val66Met involvement in ADHD, Sanchez-Mora et al. [268] performed a meta-analysis of published data and described unpublished case-control data from four different centres in Germany, the Netherlands, Norway, and Spain, with a total of 1445 adult ADHD patients and 2247 gender-matched healthy controls. They obtained no association between the p.Val66Met polymorphism and ADHD in the pooled sample; nor did they observe any overall gene effect for the disorder after controlling for gender effects and co-morbidity with mood disorders.

Aureli et al. [269] genotyped paediatric patients presenting ADHD and/or intellectual disability for the Val66Met and 270 C/T polymorphisms in BDNF. The notion of intellectual disability encompasses various cognitive deficits, including mental retardation, deficits too mild to properly qualify as mental retardation, various specific conditions (e.g., learning disability), and problems acquired later in life through acquired brain injuries or neurodegenerative disorders, including dementias; these may appear at any age. The diagnosis of ADHD and intellectual disability was confirmed by the clinicians in accordance with DSM-IV criteria. They observed that the G/A genotype of the Val66Met SNP was associated with both ADHD and intellectual disability, and further that the G allele was significantly associated with ADHD. The C/C genotype of the C270T SNP was significantly overrepresented in ADHD and intellectual disability groups compared with the controls. These findings suggested that both BDNF polymorphisms could play a role in the etiology

of ADHD [269]. From another perspective, van Beijsterveldt et al. [270] have developed a parental-assessment report at ages 3, 7, 10, and 12 years over more than 16,000 twin pairs that 1148 genotyped children presenting attention disorder, a cornerstone of ADHD. They developed a longitudinal framework to test genetic association effects with 26 SNPs of genes encoding for several putative contributors to ADHD, including HTR2A, COMT, TPH2, and BDNF. They found that the broad heritability for the AP latent factor was 82%, and the latent factor explained around 55% of the total phenotypic variance, yet none of the SNPs showed a significant association with attentional problems.

The most commonly applied instrument for ADHD diagnosis is the CPT. As noted earlier, in a typical CPT set-up, an individual sits in front of a computer terminal and is required to press (or not press) certain keys depending on the stimulus that flashes on the screen. Good performance requires individuals to sustain their attention to a selectively boring task and to refrain from impulsive responding. Performance measures of individuals with ADHD are compared to performance by appropriate control individuals. Thus, the CPT in conjunction with genotyping, provide important tools for defining ADHD gene involvement. For example, Dresler et al. [271] applied the CPT to examine the influence of the common 9- and 10-repeat alleles of SLC6A3 on prefrontal brain functioning and cognitive response control in a large sample of adult ADHD patients (n=161) and healthy controls (n=109). Within the group of ADHD patients, nine-repeat allele carriers showed significantly reduced cognitive response control, whereas no influence of SLC6A3 genotype was observed in the control group. In contrast to previous association studies of children, the nine-repeat-not the 10-repeat-allele was associated with functional impairments in their sample of adult ADHD patients. In this respect, Cho et al. [272] evaluated the effects of the adrenergic α -2A receptor (ADRA2A) and BDNF gene-gene interaction on CPT performance, measuring individuals' sustained and selective attention, and impulsiveness, in a Korean population with ADHD. In total, 122 ADHD participants (8.6±2.3 years, 104 boys and 18 girls) completed the CPT. They genotyped the DraI polymorphism of ADRA2A (rs583668) and rs11030101 polymorphism of BDNF, and obtained significant interaction effect of the ADRA2A rs553668 and BDNF rs11030101 for response time variability of the CPT. This study thus offered preliminary evidence for the effect of the BDNF and ADRA2A gene-gene interaction on performance on the CPT in ADHD.

Epigenetic Regulation of Intervention

Therapeutic intervention in ADHD is complicated by marked comorbidity within symptoms domains that have linked the disorder with academic underachievement, substance abuse and dependence, psychosocial problems and social maladjustment, unemployment in adulthood, as well as executive dysfunctioning and borderline personality disorder [273-275]. In this vein, several twin studies have reported that the covariation ADHD and combined ODD/CD symptoms and between ADHD and CD symptoms was explained largely on the basis of common genetic risk factors [73,276-279], but not always (e.g., [280]). Nevertheless, although inattentive and hyperactive-impulsive symptoms were likely influenced by common as well as specific genetic risk factors, certain family environmental risk factors have been discussed for this area of comorbidity [281]. Tuvblad et al. [282] examined the genetic and environmental correlations among ADHD, ODD, and CD in 1219 twins (aged 9-10 years) that included 605 families from the larger Los Angeles community. Externalizing behavior, i.e., aggression, delinquency, and hyperactivity [283], was reported to explain the covariance among those disorder symptoms.

The authors have indicated that genetic influences explained more than half of the variance in the externalizing factor but that there were unique genetic and environmental influences in each set of symptoms. Vanyukov et al. [284] found that the strength of association between ADHD, CD, ODD, and parenting index depended on the MAOA genotype (whether low-activity or high activity), and parental gender (see above). MAOA polymorphism linkage with substance abuse disorders was detected when parenting was controlled for.

Genetic linkage studies of ADHD pharmacological intervention have demonstrated that associations have fitted the *drug response phenotype* rather than the disorder diagnosis (cf. [90,285]). Methylphenidate binds to the dopamine transporter and blocks its activity [286]; the behavior response to the compound may be moderated by genetic variants affecting aspects of dopamine transporter structure-function parameters. Joobert et al. [120] showed that the 3'-UTR VNTR polymorphism in the dopamine transporter gene modulated the behavior response to methylphenidate (see also [287-290]). Thakur et al. [291] assessed ADHD patients, aged 6 to 12 years (n=157) with regard to their behavior response to methylphenidate and genotyped them for the triallelic 5-HTTLPR polymorphism in the SLC6A4 gene. They obtained a significant Gene x Treatment interaction effect for CGI-parents (assessment) but not CGI-teachers. Children homozygous for the lower expressing alleles ($s+I_c=s'$) responded well to placebo without additional improvement by the compound, compared to children carrying a higher expressing allele (I_A). Kereszturi et al. [292] reported a significant role of the high activity Val-allele of COMT Val158Met polymorphism in their ADHD sample. By applying a categorical analysis of 90 responders vs. 32 non-responders, they found an association between the Val-allele or Val/Val genotype and good methylphenidate response. Analyzing symptom severity as a continuous trait, a significant interaction of COMT genotype and methylphenidate was found on the Hyperactivity-Impulsivity scale. Symptom severity scores of all three genotype groups decreased following methylphenidate administration but the Val/Val homozygote children expressed significantly less severe symptoms than those with Met/Met genotype after treatment ($p=0.015$). In a randomized, within-subject, double-blind design in which 58 ADHD children (ages 6-12 years) received placebo, 0.15, 0.3, or 0.6 mg/kg of MPH three times daily over nine weeks, Leddy et al. [293] measured percent lunch consumed as a function of dopamine-related genotypes and MPH dose. They obtained a significant dose-response reduction in eating across all genotypes measured, as well as a significant interaction of dose with DAT SLC6A3 and DRD2 genotypes. Additionally, Cheon et al. [294] have shown existence of an association between the 4-repeat allele at DRD4 and good response to MPH in Korean ADHD children. Palmason et al. [295] showed that the Met allele of the COMT Val(158)Met SNP was associated with increased ADHD symptom severity, without co-morbid CD. ADHD symptom severity and early adverse familial environment were positive predictors of lifetime, thereby emphasizing the need for early intervention. Finally, high levels of comorbidity of ADHD with other disorders strongly suggests complex epistatic or pleiotropic effects acting in common with the environmental influences [296,297].

In studies of ADHD, dysfunctional and dysregulated neurotransmitter systems, e.g., dopamine, have been linked to impairments of sustained (continuous performance) attention, inhibitory control, and working memory [298]. Cognitive and neurobehavioral studies that focus on particular tasks, reaction time, and verbal working memory, with concomitant neuroimaging provide exhaustive criteria for ADHD endophenotypes and a bridge between

observed traits and genetic vulnerability. Bidwell et al. [299] collected DNA in 202 families consisting of at least one ADHD proband and at least one parent or sibling. They found that VNTR polymorphisms of the DRD4 and DAT1 genes were associated significantly with the ADHD phenotype. The association with DRD4 was driven by both inattentive and hyperactive symptoms, whereas the association with DAT1 was driven primarily by inattentive symptoms.

Conclusions

The epigenetic aspect to ADHD involves a multiplicity of complex genotyped entities, environmental realities, and endophenotypes that interact to express the gene structural material, the symptom-profiles inherent to disorder pathophysiology, and the eventual responses to the therapeutic intervention, namely methylphenidate. There exists much variability and conflicting evidence for the existence, or not, of genetic associations between disorder diagnosis and genes regulating the structure and function of dopamine, serotonin, and noradrenaline, and the neurotrophic factor, BDNF. Nevertheless, the results pertaining to associations between symptoms-profiles, synonymously endophenotypes, such as lack of attention, overactivity, lack of impulse control, or overeating, appear surprisingly reassuring. The genomewide association studies carried out on ADHD population samples have failed to identify replicable associations that explain plausibly the heritable variation, but twin studies have provided sufficient instruments in the development of endophenotypes, defined as alternative, more highly heritable traits that act at earlier stages of the pathway from genes to behavior.

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