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Neurobiology of Attention Deficit/Hyperactivity Disorder

DIANE PURPER-OUAKIL, NICOLAS RAMOZ, AUDE-MARIE LEPAGNOL-BESTEL, PHILIP GORWOOD, AND MICHEL SIMONNEAU

INSERM U894 [D.P.O., N.R., P.G., M.S.] Centre Psychiatrie et Neurosciences, Paris 75014, France; Service de Psychopathologie de l'Enfant et de l'Adolescent [D.P.O.], Hôpital Robert Debré, Paris 75019, France; Centre National de Génotypage [A.-M.L.-B.] CP 5721, Evry cedex 91057, France; Centre of Psychiatry and Neuroscience [P.G.], Hôpital Sainte-Anne, Paris 75014, France

ABSTRACT: Attention deficit/hyperactivity disorder (ADHD), a prevalent neurodevelopmental disorder, has been associated with various structural and functional CNS abnormalities but findings about neurobiological mechanisms linking genes to brain phenotypes are just beginning to emerge. Despite the high heritability of the disorder and its main symptom dimensions, common individual genetic variants are likely to account for a small proportion of the phenotype's variance. Recent findings have drawn attention to the involvement of rare genetic variants in the pathophysiology of ADHD, some being shared with other neurodevelopmental disorders. Traditionally, neurobiological research on ADHD has focused on catecholaminergic pathways, the main target of pharmacological treatments. However, more distal and basic neuronal processes in relation with cell architecture and function might also play a role, possibly accounting for the coexistence of both diffuse and specific alterations of brain structure and activation patterns. This article aims to provide an overview of recent findings in the rapidly evolving field of ADHD neurobiology with a focus on novel strategies regarding pathophysiological analyses. **(*Pediatr Res* 69: 69R–76R, 2011)**

Attention deficit/hyperactivity disorder (ADHD) is a highly prevalent neurodevelopmental condition, characterized by symptoms of inattention and impulsivity/hyperactivity to a degree that is inconsistent with developmental level. ADHD symptoms persist into adulthood in a majority of patients (1) and are associated with functional impairment and increased risk of depression, substance abuse, and antisocial behavior. Clinical presentation is heterogeneous with three subtypes identified according to the most prevalent symptoms (primarily inattentive, primarily hyperactive/impulsive, and combined) and with a relative context-dependence of symptom expression although the condition has a chronic course. ADHD is associated with cognitive impairments in inhibitory control and executive function but neuropsychological profiles of subjects with ADHD, despite significantly differing from controls in group comparisons, also show considerable inter- and intraindividual variability. This clinical heterogeneity is likely to reflect the multiplicity of causal pathways leading to the development of the disorder and of a series of moderating and mediating factors involved in symptom expression. Treatment of ADHD involves pharmacologic and nonpharmacologic strategies. Catecholaminergic systems are the main targets of stimulant and nonstimulant medications used to alleviate ADHD symptoms. Convergent studies support that genetic factors are involved in the liability of ADHD symptoms (OMIM 143465). The last decade's research has pointed out various CNS abnormalities in ADHD patients, confirming the neurobiological basis of the disorder. However, there is still a lack of insight into the mechanisms linking genotypes, neural processes, and cognitive/behavioral symptoms. Recent findings point out that other neurodevelopmental disorders like autism, schizophrenia, and epilepsy share genetic variants with ADHD (2). These developments should encourage the search for relevant intermediate clinical or cognitive phenotypes that are more likely related to the underlying neurobiological mechanisms involved in ADHD symptoms than the categorical diagnosis itself. In particular, traits shared by different neuropsychiatric conditions warrant further attention (3). As neurobiology of ADHD is a rapidly evolving domain of research, this article aims to provide an update of recent findings in genetics, molecular biology, and neuroimaging and a review of the main neurocognitive and biological models of ADHD.

Genetic and Environmental Contributions to ADHD

Family studies have shown that relatives of ADHD patients are at increased risk for the disorder (4). As the familial clustering of ADHD symptoms may be accounted for by both genetic and environmental sources of transmission, twin studies were used to estimate the relative contributions of genes and environment to the phenotypic variance of ADHD in the population. Twin studies provide an estimate of heritability by comparing concordance rates of ADHD diagnosis or traits in monozygotic and dizygotic twins. They have consistently shown that genetic factors explain a large proportion of ADHD variance with pooled data from 20 twin studies providing a mean heritability estimate of 76% in children and adolescents (5). Heritability estimates in adults are lower, ~30% (6), a possible consequence of the broader environmental range in adulthood. Adoption studies are another method to test whether genetics contribute to the familial

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Correspondence: Diane Purper-Ouakil, M.D., Ph.D., INSERM U894 Centre Psychiatrie et Neurosciences, Equipe 1, 2ter rue d'Alésia, 75014 Paris, France; e-mail: diane.ouakil-purper@orange.fr

Abbreviation: ADHD, attention deficit/hyperactivity disorder; **ASD,** autism spectrum disorder; ***DISC 1,*** disrupted-in-schizophrenia gene; **GWAS,** genome-wide association study; **GxE,** gene-environment interaction; **MPH,** methylphenidate; ***SLC6A3/DAT1***, dopamine transporter gene; ***SLC6A2/NET1,*** norepinephrine transporter gene; **SNP,** single-nucleotide polymorphism

transmission of a disorder. ADHD rates have been found to be greater in biological relatives of ADHD children than in the adoptive families (7). The results of a recent meta-analysis of twin and adoption studies indicated that genetic factors accounted for 71 and 73% of the variance of inattentive and hyperactive symptoms, respectively. Nonadditive genetic effects (*e.g.* interactions between alleles across and within loci) showed stronger influences on inattention compared with hyperactivity (15 *versus* 2%), suggesting that specific etiological factors influence each symptom dimension (8).

Several environmental factors have been identified as putative risk factors for ADHD. *In utero* events such as maternal stress during pregnancy (9), prenatal exposure to tobacco, alcohol and other drugs/environmental toxins (10,11), pregnancy/birth complications (11), as well as intrauterine growth retardation and low birth weight/prematurity (12,13) have been associated with ADHD. Early postnatal environmental influences related to ADHD or core ADHD symptoms include neonatal anoxia and seizures, brain injury (11), exposure to lead (14), and polychlorinated biphenyls (15). Psychosocial adversity and high levels of family conflict were also associated with ADHD (16,17). Recent findings have related ADHD to more specific familial issues such as inconsistent parenting after controlling for parental ADHD (17), marital, and children's negative appraisal of family conflict (18). Children having suffered early institutional deprivation for a duration of 6 mo or above show high levels of ADHD-like symptoms, but in this population, inattention/hyperactivity was also strongly linked to attachment disorders (19).

Recent studies have taken into account genetic factors that may contribute to adverse prenatal and later life circumstances (*i.e.* smoking during pregnancy or stress during pregnancy might be more frequent in mothers with ADHD). A comparison of siblings differing for their exposure to prenatal nicotine showed that the association of smoking during pregnancy on subsequent ADHD in the child was reduced but remained significant by controlling for genetic and environmental confounds (20). A study of pregnant mothers related or unrelated to their child as a result of *in vitro* fertilization showed that prenatal stress was linked to ADHD only when mothers were related to their child, suggesting that the association may be accounted for by inherited factors (21). A recent twin study focused on ADHD-related conditions (antisocial behavior and substance use disorders in young adults), has provided an important insight into mechanisms of gene-environment influence on externalizing disorders by showing that genetic factors contribute more to the development of behavioral symptoms in a context of high environmental adversity (22), in accordance with a diathesis-stress model. These examples illustrate the importance of genetically informed study designs to further disentangle environmental and genetic contributions to ADHD.

Neuropsychological Endophenotypes

The clinical and etiological complexity of ADHD as well as the small proportion of variance in ADHD symptoms explained by candidate genes has encouraged the search for endophenotypes, heritable traits thought to be more proximal to the genetic etiology of the disorder. Cognitive deficits have been consistently identified in ADHD and are potential markers for the neural dysfunctions of the disorder. Compared with controls, subjects with ADHD show deficits in executive functions, especially in tasks involving executive control (response inhibition, working memory) (23), have variable response speed (24), show delay aversion (25), and variability in motor timing (26). Cognitive deficits in ADHD have shown to persist over time, even in subjects showing remission of behavioral symptoms (27). Unaffected co-twins of ADHD performed worse than controls in a majority of neuropsychological tasks. Results showed differences in response variability, inhibitory control, and processing speed despite controlling for subclinical ADHD, suggesting that these variables meet criteria for neuropsychological endophenotypes (28). Using neuropsychological tests having previously showed significant heritability in a genome wide linkage analysis of ADHD, Rommelse *et al.* (29) found two significant genome-wide linkage signals, one for Motor Timing task on chromosome 2q21.1 (LOD score: 3.944) and one for Digit Span test on 13q12.11 (LOD score: 3.959). The examination of neuropsychological endophenotypes is a promising method to identify more homogenous subgroups of patients, increasing the possibility to detect small genetic effects and specific neurobiological mechanisms involved in the etiology of ADHD.

Molecular Genetics of ADHD

Whole genome linkage studies. Linkage studies in families with multiple affected individuals screen the genome with genetic markers. Co-segregation of markers with the disorder indicates that a particular region is likely to contain risk genes for ADHD. The LOD is an estimate of the strength of linkage and is considered significant above 3 and suggestive for linkage between 2 and 3. In the whole genome linkage studies published to date, few regions were identified in more than one study but no locus was identified in all of them. A meta-analysis of seven linkage studies identified a genome wide significant finding in the chromosome region from 16q23.1 to the q terminal (30) but no gene within this region had been previously identified in the candidate gene approaches. As linkage studies are predominantly suited to identify genetic factors of strong effect ($>10\%$ of the variance), this approach may not be able to capture small effects of specific genes.

Candidate gene association studies. Candidate gene association studies select genes on the basis of their possible implication in the pathophysiology of the disorder. Case-control association studies compare frequencies of genetic variants in controls and affected probands, whereas familial association studies search of an excess of transmission from parents to offspring.

Most of medications used for the treatment for ADHD increase the availability of catecholamines in the synaptic cleft; therefore genetic association studies examining putative risk genes have mainly focused on genes of the dopamine (DA) and norepinephrine (NE) neurotransmitter systems. In

general, genetic markers encompassing the candidate gene that are screened for association, are usually of two types: single nucleotide polymorphisms (SNPs), one nucleotide position with a bi-allelic variation, and variable nucleotide tandem repeats, a repeated sequence of nucleotides with multi-allelic variation. Table 1 summarizes main findings of association studies with positive meta-analyses (5,31–36). The most consistent evidence for a genetic association to the ADHD phenotype has been shown for markers in DA receptor D4 (*DRD4*), DA receptor D5 (*DRD5*), DA transporter (*SLC6A3/DAT1*), serotonin receptor 1B (*HTR1B*), serotonin transporter (*SLC6A4/5HTT*), and synaptosomal-associated protein 25 (*SNAP-25*) genes. The catechol-O-methyltransferase val/val genotype, although not significantly associated to the global ADHD phenotype, has been linked to conduct disorder symptoms in patients with ADHD in several independent samples (37). This finding suggests that the examination of refined phenotypes is a fruitful strategy to identify vulnerability genes of small effect in candidate gene studies of a complex condition such as ADHD.

Genome-wide association studies. Genome-wide association study (GWAS) studies, by testing >100,000 SNPs distributed across the genome for association with a disorder, offer a hypothesis-free approach to identify genetic variants in complex diseases. These studies have been successful for a variety of neurodevelopmental and neurodegenerative diseases such as autism, schizophrenia, and Alzheimer. However, most of associated SNPs have a small effect size and the proportion of heritability explained is at best modest (38). GWAS studies have only recently been used in ADHD and none of these first studies showed robust SNP associations in the primary analyses (39–41). This suggests that a variety of alleles may be associated with ADHD but each of them with a small effect size requiring further association studies with sufficient statistical power through increased sample size or identification of more homogenous intermediate phenotypes. Although the findings of the first ADHD-GWAS studies were not significant at the genome-wide level, analysis of high ranking SNPs yielded evidence for genes involved in basic neurobiological processes such as cell architecture and com-

Table 1. *Main findings of genetic association studies*

Gene	Most studied genetic variations	Function of protein	Positive meta-analysis
Dopaminergic genes			
DRD4	Seven repeat allele of a 48-bp VNTR in exon 3	DA receptor	OR = 1.34 (31)
	Polymorphism in the promoter region, allele-521T>C		OR = 1.21 (32)
DRD5	148 bp microsattelite marker	DA receptor	OR = 1.3 (31) OR = 1.23 (32)
SLC6A3/DAT1	10-repeat allele of a 40-bp VNTR in the 3′ UTR of exon 15	DA transporter	OR = 1.12 (32) OR = 1.17 (36)
	Three-repeat allele of a VNTR located in intron 8 polymorphism in the		OR = 1.25 (32)
	3′UTR, allele 328G>A		OR = 1.20 (32)
DBH	Taq 1 restriction site polymorphism in intron 5	Conversion of DA to NE	No
MAO-A	Four- or five-repeat variant of a 30 bp VNTR in the promoter region.	Metabolism of NE, DA, and 5-HT	No
DRD2/DRD3	Different alleles studied	DA receptors	No
COMT	Val108Met polymorphism	Catabolism of NE, DA	Negative OR = 0.95 (35)
Noradrenergic genes			
ADRA2A	SNP located in the promoter region, allele-1291C>G	NE receptor	No
ADRA2C	Dinucleotide repeat poly-morphism located 6 KB from the gene	NE receptor	No
SLC6A2/NET	Several SNPs (introns 7, 9, 13; exon 9, promoter)	NE transporter	No
Serotoninergic genes			
HTR1B	SNP (861G>C) exon1	5-HT receptor	OR = 1.11 (32)
			OR = 1.35 (33)
HTR2A	Polymorphisms T102C, G1438A, His452Tyr	5-HT receptor	No
SLC6A4/5HTT	44 bp insertion/deletion	5-HT transporter	OR = 1.17 (32)
	Polymorphism (HTTLPR) in the promoter region		OR = 1.31 (5)
TPH-2	Several SNPs	Rate-limiting enzyme in the synthesis of 5-HT	No
Gene	Most studied genetic variations	Function of protein	Positive meta-analysis
Other candidate genes			
SNAP25	SNP T1065G at the 3′ end of the gene	Regulation of neuro-transmitter release	OR = 1.15 (32)
			OR = 1.19 (34)
CHRNA4	Intron 1 dinuleotide repeat and several SNPs	Alpha-4 subunit of nicotinic acetylcholine receptors	No
GRIN2A	SNP in exon 5	Subunit of the N-Methyl D-Aspartate receptor	No
BDNF	Substitution Val to Met at codon 66, allele Val66	Protein supporting neuronal survival, growth, differentiation	No

VNTR, variable nucleotide tandem repeat; UTR, untranslated region; DBH, dopamine-beta-hydroxylase; MAO-A, monoamine oxidase A; COMT, catechol-O-Methyltransferase; HT, serotonin; ADRA2A, alpha-2-A adrenergic receptor; ADRA2C, alpha-2-C adrenergic receptor; TPH-2, tryptophane hydroxylase; SNAP 25, 25kD synaptosomal protein; CHRNA4, nicotinic alpha 4 receptor; GRIN2A, glutamate receptor, ionotropic, *N*-methyl D-aspartate 2A; NMDA, *N*-méthyl D-Aspartate; BDNF, brain-derived neurotrophic factor.

munication (42). If confirmed, these findings may extend future research from neurotransmitter systems to brain development, maturation, neuronal migration, and plasticity.

Search for copy number variants. Strong evidence suggests that rare mutations of large effect may be responsible for a substantial proportion of the heritability of complex diseases (43). Recent studies scanned the genomes of United States, British, and Icelandic patients with ADHD for deleted or duplicated regions, known as copy number variants (2,44). It may be expected that a copy number variant on one allele can directly affect the dosage of contained genes by minus 50% (deletion) or plus 50% (duplication). Such a dosage effect can be hypothesized as causal in human diseases. Importantly, both repertoires recently identified in ADHD are significantly enriched for genes known to be important for psychological and neurological functions, including learning, behavior, synaptic transmission, and CNS development. Furthermore, they overlap with repertoires previously identified in autism (45), schizophrenia (46), and epilepsy (47).

Gene-environment interactions. Gene-environment interactions (GxE) operate in two ways: 1) a genetic factor may enhance or diminish the impact of a particular environment and 2) an environmental factor may activate a genetic effect. GxE may account for a significant proportion of the clinical heterogeneity of ADHD by increasing phenotypic variance beyond main effects of genes and environment (48). GxE has been reported between various genetic variants and environmental factors such as maternal smoking and maternal alcohol use during pregnancy, LBW, season of birth, and psychosocial adversity (49). Some of these GxE findings failed to be replicated but globally, results appear to be more consistent for psychosocial factors compared with prenatal/early environmental factors (49) and compatible with a diathesis-stress model according to which genetic factors have more impact on ADHD in at-risk environments (50).

Pharmacological Treatments and Neurobiology of ADHD

Pharmacological treatments of ADHD all optimize catecholamine signaling in the prefrontal cortex. Mechanisms of action of stimulants [methylphenidate (MPH) and amphetamines] include blockade of the DA SLC6A3/DAT and NE transporters SLC6A2/NET, inhibition of monoamine oxidase and enhanced release of catecholamines (51). Stimulants mainly act on DA D1 receptors in the prefrontal cortex and on D2 receptors in the striatum. Atomoxetine, a nonstimulant drug used in ADHD, blocks the NE transporter and increases levels of both NA and DA in the prefrontal cortex. Guanfacine, another nonstimulant drug acts at postsynaptic alpha-2A receptors to enhance NE transmission. Therapeutic effects of DA stimulation is thought to involve a weakening of inappropriate network connections (*i.e.* producing a decrease of "noise") whereas enhanced NE transmission may function by strengthening appropriate connections (*i.e.* producing an increase of "signal") (52). Current knowledge about the neurobiological mechanisms of pharmacological treatments of ADHD suggest that despite some overlap, medications show differential effects with stimulants having broad effects on attention deficits and motor symptoms and nonstimulants likely to have a more specific action in the prefrontal cortex. Recent developments in therapeutic research have extended the range of medications for the treatment of ADHD. Further research is likely to improve targeting treatments to individual symptom patterns, developmental level, and possibly to brain maturation status.

Improving adjustment of treatments to individual needs is also the aim of pharmacogenetic approaches. Pharmacogenetic studies search for genetic factors involved in the pharmacodynamics and pharmacokinetics of drugs that could explain the interindividual variability of treatment response or tolerance. A meta-analysis of *SLC6A3/DAT1* pharmacogenetic studies on a total of 475 subjects showed a significant association between the 10 and 10 genotype of the 40-bp variable nucleotide tandem repeats and low rates of MPH response (53). Recently, a variant of the carboxylesterase 1, the principal enzyme that metabolizes MPH, was found associated with dosages needed to obtain treatment response; heterozygote patients (Gly/Glu) needed lower doses for optimal treatment effects compared with homozygotes (Gly/Gly) (54). To date, only one GWAS was performed on MPH treatment response but failed to identify markers meeting criteria for statistical significance for GWAS (55). Two studies screened the pharmacogenetic effect of on cytochrome P450 2D6 (*CYP2D6*) and *SLC6A2/NET1* genes. The first showed that specific alleles of the *CYP2D6* gene involved in rapid or poor metabolism were associated with a lower or a greater reduction in ADHD symptoms, respectively (56). The second study on two cohorts of patients, identified polymorphisms in the *SLC6A2/NET1* gene in the clinical response of atomoxetine in ADHD (57). Coupled analyses of clinical response to pharmacological interventions, pharmacogenetics, and brain functioning imaging, as proposed by Szobot *et al.* (58) are likely to further improve knowledge about ADHD and its treatment.

Brain Phenotypes in ADHD

Insights from neuroimaging. A variety of brain subregions including frontal and parietal cortexes, basal ganglia, cerebellum, hippocampus, and corpus callosum were found impacted in ADHD (59). These regions have been involved in the functional networks related to ADHD (Fig. 1). A detailed review of these networks indicates that diffuse and more specific alterations in brain structures and neural networks are possibly combined in ADHD and lead to organized brain phenotypes (60). For example, a study of functional MRI in children and adolescents with ADHD showed decreased connectivity in a fronto-striato-parieto-cerebellar network. This connectivity was normalized by MPH except in the parieto-cerebrellar functional circuit (61). New techniques such as diffusion tensor imaging using the direction of diffusion of water molecules to infer the orientation of white matter tracts in the brain have shown preliminary evidence for dysfunctions in anatomical connections in ADHD (62).

Over the past 2 decades, MRI allowed to study developmental trajectories of brain morphometry in patients with

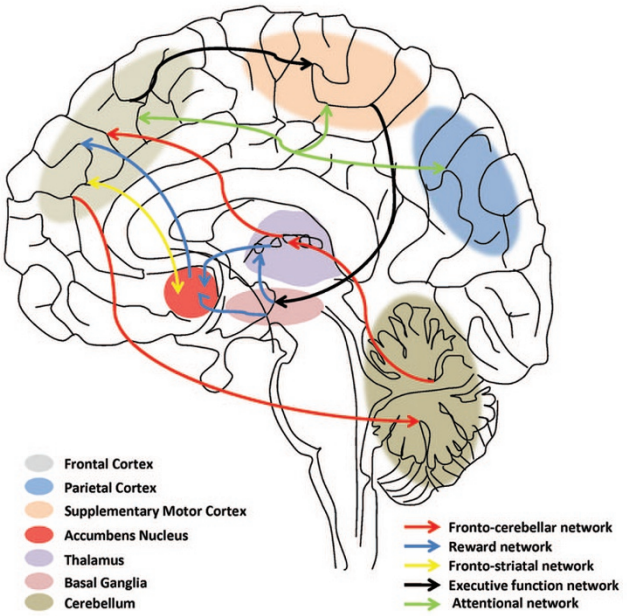

Figure 1. Schematic representation of functional circuits involved in the pathophysiology of ADHD. Here are summarized the attentional network (*green*), the fronto-striatal network (*yellow*), the executive function network (*black*), the fronto-cerebellar network (*red*), and the reward network (*blue*).

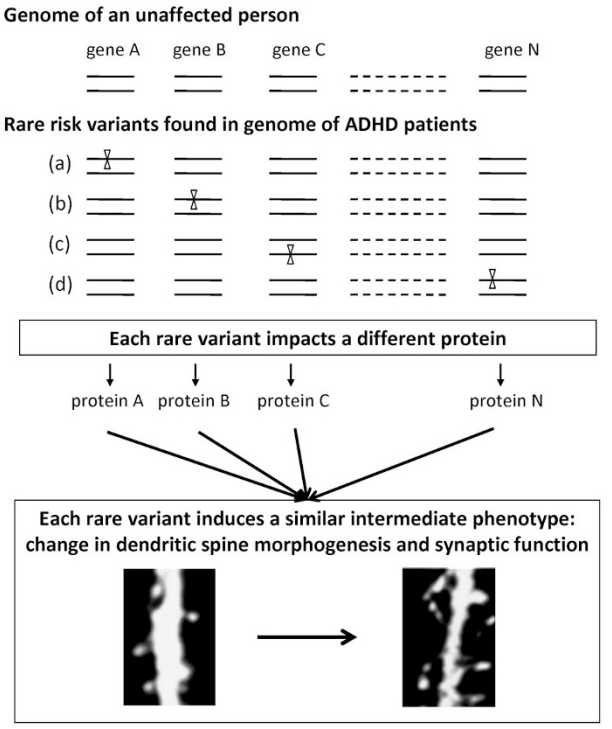

Figure 2. A same intermediate phenotype can be generated by variants identified in many genes. The figure illustrates how a variety of genes could have a similar impact on protein complexes neuronal structures such as the dendritic spine. Similar changes in dendritic spine morphology could constitute an intermediate phenotype involved in abnormal synaptic transmission.

ADHD compared with controls. These longitudinal studies have shown a developmental delay of cortical thickness in ADHD, with greatest differences between ADHD and controls in maturation of the middle prefrontal cortex. Interestingly, normalization of volumes in different brain regions such as the parietal cortex and the hippocampus parallel clinical improvement of symptoms, whereas progressive volume loss of cerebellar regions and hippocampus were associated with persistent symptoms (59).

Imaging studies are also beginning to study familial patterns of brain structure and function. Brain endophenotypes refer to brain characteristics shared by ADHD patients and their siblings and likely to be involved in the liability to the disorder. Activation pattern of the ventral prefrontal cortex and reduced striatal activity have been identified as possible brain endophenotype candidates (63,64).

Neurocognitive models of ADHD. The dual pathway model of ADHD (25,65) links inattention and deficits in executive functions to impairments in prefrontal-striatal circuits whereas hyperactivity may be consecutive to dysfunctions of reward response and motivation, related to a frontal-limbic system. Multiple pathways to ADHD symptoms are also pointed out in another model suggesting that a poor adjustment of behavior to environmental cues may arise from deficient signaling of the prefrontal cortex by subcortical and posterior systems (*i.e.* a failure to detect discrepancies between current and expected context because of a failure in bottom-up mechanisms) or from an intact signaling but inefficient top-down control (66,67).

From genes to brain structure and function. Striatal activation patterns have been linked to DAT1 genotype through higher levels of DAT expression in carriers of the 10-R allele (64). Gene effects have also been shown on brain structure with DRD4 and DAT1 genotypes influencing the volume of the prefrontal cortex and the volume of the caudate nucleus, respectively (68). Neuroimaging methods may not only contribute to further document gene effects on brain function and structure but also provide insight into environmental or GxE effects in the near future (69).

Recent genetic findings suggest that a variety of genes could have, *via* their rare variants, a similar impact on protein complexes. Modifications of proteins in neuronal structures such as the dendritic spine could account for an intermediate phenotype (*i.e.* changes in dendritic spine morphology) leading to an abnormal synaptic transmission. Such molecular and subcellular phenotypes can be common to a variety of distinct rare variants (Fig. 2). A key issue for future research is to understand how a diversity of neuropsychiatric phenotypes can be generated by overlapping genotypes.

Novel strategies for pathophysiological analyses of ADHD. Animal models are one of the most promising approaches to study molecular pathophysiology of ADHD. If models that may recapitulate the full phenotypic spectrum of a psychiatric disorder are currently out of reach, creation of phenotypic components is feasible (70). Table 2 illustrates the main animal models related to ADHD (71–75).

New perspectives are expected from using top-down and bottom-up cognitive paradigms in experiments with primates. Such paradigms can be transposed to rodents allowing experimental analysis of the role of the prefrontal cortex in decision making using models attainable to genetic modifications (76).

Table 2. *Principal animal models related to ADHD*

Model	Molecular basis	Hyperactivity	Impulsivity	Stereotype behavior	Pathophysiology
Rat SHR (71)	160 bp insertion in the 3′-UTR region of *DAT 1*	+	+	−	Hypofunctional DA synapses Hyperfunctional NE synapses
Snap 25 −/− mouse (72)	KO of *Snap25* gene (spontaneous mutation)	+	+	−	Hyperfunctional NE synapses
DAT−/− mouse (73)	KO of *DAT1*gene	+	?	+	Hypofunctional DA synapses (phasic release)
β2 −/−mouse (74)	KO of the gene of β2 sub unit of the central nicotinic receptor	+	+	−	Presynaptic nicotinic receptors facilitating phasic dopamine release
Fmr1Mouse (75) KO of the *Fmr1*gene	+	+	?	?	Deregulation of dopaminergiques D2 receptors

SHR, spontaneous hypertensive rat; UTR, untranslated region; *DAT1*, gene of the dopamine transporter; SNAP-25, 25 kD synaptosomal associated protein; KO, knock-out; Fmr1, fragile x mental retardation 1.

Such approaches can be instrumental in a near future to dissect molecular mechanisms involved in executive function networks and their defects in ADHD.

Another promising development relates to models mimicking human mutation and chromosomal rearrangements that have been recently generated for both autism spectrum disorders (ASDs) and schizophrenia. For ASDs, one of the neuroligin-3 mutations identified in patients with ASDS was introduced into mice. The mutant mice showed impaired social interactions but enhanced spatial learning abilities. Unexpectedly, these behavioral changes were accompanied by an increase in inhibitory synaptic transmission with no apparent effect on excitatory synapses. Chromosomal engineering was used by to generate a large duplication in chromosome 15q11–13 seen in ASDs (77). Mice with a paternal duplication display poor social interaction, behavioral inflexibility, abnormal ultrasonic vocalizations, and correlates of anxiety. Furthermore, abnormal serotonin neurotransmission was reported.

For schizophrenia, a mouse model mimicking disrupted-in-schizophrenia 1 (*DISC1*) translation was generated by Kvajo *et al.* (78). A balanced chromosomal translocation segregating with schizophrenia and affective disorders in a large Scottish family (79) implicated *DISC1* as a susceptibility gene for major mental illness. Kvajo *et al.* (78) used a disease-oriented approach to generate mutant mice carrying a truncating lesion in the endogenous *DISC1* orthologue that models the only well-defined *DISC1* schizophrenia risk allele. This approach preserves the endogenous spatial and temporal expression pattern of the gene, thus preventing the induction of neomorphic phenotypic features. A comprehensive analysis of these mice implicates malfunction of neural circuits within the hippocampus, including synaptic plasticity changes, and medial prefrontal cortex contributing to the genetic risk conferred by the *DISC1* gene.

Conclusion

ADHD being a prevalent and chronically impairing condition, a better knowledge of neurobiological mechanisms underlying symptoms and cognitive characteristics is likely to help in optimizing current treatment options and developing novel medications and behavioral/cognitive strategies. Major advances have been made in several domains of neurobiological research.

- Improved insight into the interplay of genetic and environmental factors in the development of ADHD through genetically informed studies of risk factors.
- Identification of valid neuropsychological endophenotypes contributing to the definition of more homogeneous subgroups of patients to improve the power of genetic studies and facilitate the access to the neural basis of cognitive impairments.
- Molecular genetic studies have shown the implication of common genetic variants but their small effects on the variance of the ADHD phenotype calls for improvements in research strategies (reduce heterogeneity, increase sample sizes). Low-frequency variants have also been associated with ADHD and indicate that some genetic factors may be shared across a number of neurodevelopmental disorders.
- The ongoing studies about mechanisms of action of pharmacological treatments and the development of pharmacogenetic studies will carry opportunities for individually and developmentally tailored treatments for ADHD symptoms.
- Imaging studies have documented alterations in brain structures and functional networks, suggesting that ADHD involves both cortical dysfunction and abnormal connectivity. Several brain structures show maturational delays in anatomic brain developmental studies and brain development patterns that have been correlated with clinical and functional outcome. Similarly, recent models based on imaging and neuropsychological data have proposed links between main symptom dimensions of ADHD and impairments in specific brain circuits.

Our overview of recent trends in neurobiology of ADHD shows promising domains of research including further exploration of refined phenotypes, treatment response/outcome patterns, impact and mechanisms of action of environmental factors, and search for both common and rare genetic variants with samples and methods appropriate to the study of complex diseases. Development of new techniques of brain imaging such as DTI and functional MRI has provided preliminary

evidence for functional and anatomical abnormalities in patients with ADHD.

Recent findings in molecular genetics indicate that, although it is important to improve knowledge about brain macrostructure, a move toward studies exploring basic mechanisms involved in brain microstructure is warranted. In this regard, identification of the functional changes contributing to ADHD (through changes in the protein's code or changes in gene transcription) is another crucial issue for future research.

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