Review article

The neurobiology of attention deficit/hyperactivity disorder

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ABSTRACT

ADHD is a brain based disorder with structural and functional abnormalities in widespread but specific areas of the brain. The most significant and consistent structural imaging findings include smaller total brain volumes, and reduced volumes in the right frontal lobe, right parietal cortex, caudate nucleus, cerebellar hemispheres, and posterior-inferior lobules of the cerebellar vermis. ADHD involves hypofunction of catecholaminergic circuits, particularly those that project to the prefrontal cortex. A minimum of 18 genes have been reported to be associated with the disorder; among them the DRD4 7-repeat allele has been found associated with a thinner prefrontal and posterior parietal cortex. Epigenetic factors acting during critical periods of prenatal and postnatal development may interact with genetic determinants. Methylphenidate, as well as the catecholaminergic nonstimulant atomoxetine, are effective in improving ADHD symptoms.

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1. Introduction

Attention deficit/hyperactivity disorder (ADHD), one of the most common neurobehavioural disorders with onset in early childhood, is a highly heritable condition with documented brain abnormalities, with prominent associated symptoms and impairments that affect several aspects of the daily life function.¹ The areas of impairment associated with childhood ADHD include academic and social dysfunctions and skill deficits. Adolescents with ADHD are at high risk for low self-esteem, poor peer relationships, smoking and substance abuse.²–⁸

ADHD is a multifactorial neurobiological disorder caused by the confluence of many genetic and environmental risk
factors, each having a small effect on increasing vulnerability to the disorder. Individuals with ADHD present difficulties in several domains of attentional and cognitive functions: problem solving, planning, orienting, alerting, cognitive flexibility, sustained attention, response inhibition, and working memory.\(^9,10\) Other domains involving affective components, such as motivation and delay aversion, are also affected.\(^11-13\) Psychiatric comorbidities with childhood ADHD include oppositional defiant disorder, mood and anxiety disorders, learning disorders, tics, and mental retardation. Recently, neuroimaging has caused several important advances in the understanding of the neurobiology underlying the clinical picture of ADHD, showing that there is a clear brain basis to the disorder in regions involved in attention and executive control.\(^14,15\) Knowledge about neurobiology offers child neurologists a valuable framework to interpret clinical findings of children meeting the criteria for diagnosis of ADHD.\(^1\) In this article we provide a brief overview of the salient neurological aspects of ADHD.

### 3. Genetics

Family studies and adoption studies of ADHD have consistently supported the strong familiar nature of this disorder.\(^29\) Based on numerous studies of monozygotic twins, the mean heritability for ADHD was shown to be 77%.\(^30\) Many different, probably interacting genes, each with a very small effect size, contribute to the neurological phenotype. A minimum of 18 ADHD susceptibility genes,\(^31\) including dopamine receptors D4 and D5, dopamine transporter, serotonin receptor 1B and SNAP-25 have been reported to be associated with the

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disorder, and a number of these have been replicated in multiple studies.\textsuperscript{32} Genome scan studies on potential alleles for ADHD have demonstrated linkage on chromosomes 2q24, 5p13, 6q14, 16p13, and 17p11.\textsuperscript{33} By far, the gene most strongly implicated in ADHD is the 7-repeat allele of the human dopamine receptor D4 gene (DRD4), suggesting a strong dopamine role in the pathogenesis of ADHD.\textsuperscript{29}

Sometimes ADHD is symptomatic, and it can be related to some established neurogenetic disorders, like Tuberous Sclerosis Complex, Neurofibromatosis I, Turner Syndrome, Williams Syndrome, Velocardiofacial Syndrome (VCF), Prader–Willy Syndrome, and Fragile X Syndrome. Children with Williams Syndrome seem to be more hyperactive, whereas children with VCF tend to be more inattentive. The very high prevalence of ADHD in VCF male children (41%) suggests that the 22q11 deleted region harbors gene or genes that contribute to the etiology of ADHD in this population; recently, an association between the low level of catechol-o-methyl-transferase (COMT) 158 met allele located in this region and ADHD in VCF males has been reported.\textsuperscript{34} Children with NF1 may be more likely to fulfill diagnostic criteria for attention deficit disorder without hyperactivity.\textsuperscript{35} High rates of hyperactivity with attention impairment with oppositional behavior have been reported in tuberous sclerosis.\textsuperscript{36} The most common DSM-IV diagnosis among the fragile X boys is ADHD (73%), followed by oppositional defiant disorder, anxiety disorders.\textsuperscript{37}

4. Environmental risk factors

Several biological and environmental factors have been proposed as risk factors for ADHD, including fetal alcohol exposure, maternal smoking during pregnancy, low birth weight, food additives, lead contamination.\textsuperscript{38–41} Prenatal alcohol exposure is known to induce brain structural anomalies especially in the cerebellum.\textsuperscript{42} Children exposed prenatally to alcohol can become hyperactive, disruptive, impulsive, and are at an increased risk for a range of psychiatric disorders.\textsuperscript{43,44} Maternal smoking produces a 2.7-fold increased risk for ADHD\textsuperscript{45} and a dose-response relationship between maternal smoking during pregnancy and hyperactivity has been reported.\textsuperscript{46} Nicotinic receptors modulate dopaminergic activity, and dopaminergic disruption is believed to be involved in the pathophysiology of ADHD.\textsuperscript{47,48} Nicotine exerts its effects on various neurotransmitter systems and may induce regionally specific abnormalities in cell proliferation and differentiation.\textsuperscript{47}

5. Gene–environment interactions

Recent studies focused on the joint effects of gene variants (in DRD4 and DAT1) and prenatal substance exposures on subtypes of ADHD children, demonstrating that smoking during pregnancy is associated with the combined ADHD type in genetically susceptible children.\textsuperscript{49}

A significant interaction between DAT1 genotype and prenatal smoke exposure was found in males with prenatal smoke exposure. The patients homozygous for the DAT1 10-repeat allele had higher hyperactivity-impulsivity than males from all other groups.\textsuperscript{50}

Despite the heterogeneity of the etiology and pathophysiology of ADHD, abnormal DAT density seems to be common among subjects with ADHD.\textsuperscript{51}

6. Neuroimaging

The most significant and consistent structural imaging findings in children with ADHD include smaller total brain volumes and reduced volumes, in the right frontal lobe, caudate nucleus, the cerebellar hemisphere and posterior-inferior lobules of the cerebellar vermis.\textsuperscript{52} These early abnormalities of regional brain volumes have also been shown to change over time in children and adolescents with ADHD.\textsuperscript{53,54} Developmental trajectories study showed that volumetric abnormalities in the cerebral and cerebellum persisted with increasing age, whereas caudate differences versus normal subjects disappeared.\textsuperscript{53,55} Cortical development in children with ADHD shows a marked delay in brain maturation; the gray matter peaks were about 3 years later than in healthy controls. The delay is most prominent in prefrontal regions important for control of cognitive processes including attention and motor planning.\textsuperscript{54,56} Functional neuroimaging studies offered new data to map the brain systems involved in the ADHD, to integrate these findings with clinical symptoms, and to understand mechanism of treatment response.\textsuperscript{54,57} The recruitment of alternative networks by ADHD children to cope with functions that are particularly difficult for them may reflect the neural correlates of differences in specific neuropsychological mechanisms.\textsuperscript{58} Recent fMRI finding of right parietal dysfunction suggests a widespread maturational deficit that may be independent from the developmental stage.\textsuperscript{59}

fMRI studies also show promise for understanding mechanisms of treatment response.\textsuperscript{57,60–63} Positron emission tomography studies have shown that methylphenidate hydrochloride blocks DAT and that extracellular dopamine increases in proportion to the level of blockade and to the rate of dopamine release. This process is associated with an enhanced perception of the external stimulus as a salient in subjects with ADHD.\textsuperscript{62}

7. Treatment

The frontal-subcortical circuits (lateral prefrontal cortex, dorsal anterior cingulated cortex, caudate, and putamen) associated with ADHD are rich in catecholamines, which are involved in the mechanism of action of medications used to treat this disorder. Neuropharmacological studies provide evidence that ADHD involves dysregulation of both noradrenaline and dopamine neurotransmitter systems.\textsuperscript{64} Dysregulation of a noradrenaline system is suggested to lead to inefficient function of the posterior cortical attentional system, while dopamine dysregulation leads to impaired function of the anterior executive system\textsuperscript{65} (see Fig. 1).

Strong evidence exists indicating that the stimulant medications, such as methylphenidate (MPH) and dextroamphetamine,
as well as the catecholaminergic nonstimulant atomoxetine (ATX), are effective in improving ADHD symptoms. Treatment with MPH and ATX both significantly increase activation in key cortical and subcortical regions subserving attention and executive functions. Therefore, alterations in dopaminergic and noradrenergic function are apparently necessary for the clinical efficacy of pharmacological treatment of ADHD. However, MPH and ATX have both common and distinct neural effects, consistent with the observation that many children respond well to both treatments, and some respond preferentially to one or the other.

Even though pharmacogenetic studies of ADHD are in the early stages, there could be a correlation between the response to MPH and polymorphism of the DRD4 gene, together with an interaction between polymorphism at DRD4 and 5-HTT genes in the response to MPH. Psychopharmacological options improve not only abnormal behaviors of ADHD but also self-esteem, cognition, and social and family functioning. Psychotherapy combined with medication may play role in treating behavioural problems, organizational issues and psychiatry comorbidities.

Although pharmacotherapy for ADHD appears to prepare and facilitate the brain for learning, experiential programs need to elicit compensatory development in the brain. The clinical amelioration of some children after environmental experiential inputs, and early cognitive/behavioral treatment could indicate outcome-associated plastic brain response. One year treatment with MPH may be beneficial to show enduring normalization of neural correlates of attention. Little is known about the long-term effects of stimulants on the functional organization of the developing brain. Recent findings have shown that chronic methylphenidate on drug-naive boys with ADHD enhanced neuropsychological functioning on “recognition memory” component tasks with modest executive demands.

8. Future directions

The exciting findings that link the genomic, structural and functional changes in the brain constitute a convincing emerging brain model of dysfunctions in ADHD. Functional imaging studies have made great progress in helping to uncover the neural substrate of ADHD. The virtual explosion of new knowledge provided by the field of cognitive neuroscience regarding the brain’s attention system combined with the rapid pace of technological advances promises to make the next few years exciting times for unraveling the mysteries of the neurobiology of ADHD. It is hoped that advances in understanding the underlying neurobiology of ADHD will contribute to identifying more specific and targeted pharmacotherapies, and will help child neurologist to better manage their patients.

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