Review

Developmental Neuroscience

Dev Neurosci 2009;31:36–49
DOI: 10.1159/000207492

Received: March 25, 2008
Accepted after revision: September 11, 2008
Published online: April 17, 2009

Towards Conceptualizing a Neural Systems-Based Anatomy of Attention-Deficit/Hyperactivity Disorder

Nikos Makris[a–c] Joseph Biederman[a] Michael C. Monuteaux[a]
Larry J. Seidman[a, d]

[a]Harvard Medical School Department of Psychiatry and [b]Center for Morphometric Analysis, Harvard Medical School Department of Neurology, Massachusetts General Hospital, [c]Department of Anatomy and Neurobiology, Boston University School of Medicine, and [d]Public Psychiatry Division of the Beth Israel Deaconess Medical Center, Harvard Medical School Department of Psychiatry, Massachusetts Mental Health Center, Boston, Mass., USA

Key Words
Attention-deficit/hyperactivity disorder · Magnetic resonance imaging · Diffusion tensor imaging · Neural systems · Executive function · Attention · Impulsivity · Neuroanatomy

Abstract
Convergent data from neuroimaging, neuropsychological, genetic and neurochemical studies in attention-deficit/hyperactivity disorder (ADHD) have implicated dysfunction of the dorsolateral prefrontal cortex (DLPFC) and dorsal anterior cingulate cortex (dACC), which form the cortical arm of the frontostriatal network supporting executive functions. Furthermore, besides the DLPFC and dACC, structural and functional imaging studies have shown abnormalities in key brain regions within distributed cortical networks supporting attention. The conceptualization of neural systems biology in ADHD aims at the understanding of what organizing principles have been altered during development within the brain of a person with ADHD. Characterizing these neural systems using neuroimaging could be critical for the description of structural endophenotypes, and may provide the capability of in vivo categorization and correlation with behavior and genes.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) refers to an early-onset highly prevalent neurobehavioral disorder with genetic, environmental and biological etiologies, which persist into adolescence and adulthood in a majority of symptomatic children of both genders (40–60%) [1]. Although ADHD is perceived by some as an American disorder, its prevalence is in the same range worldwide [2], estimated to affect 5–10% of children [2] and 4% of adults [3, 4]. It is characterized by behavioral symptoms of inattention, hyperactivity and impulsivity across the life cycle [5]. An emerging neuroimaging literature has provided strong evidence linking ADHD with deficits in key brain regions subserving attention and executive functions. Although neuroimaging studies have fundamentally contributed to the documentation of the validity of ADHD as a brain disorder, a conceptual framework providing a neural systems neuroanatomy of this disorder has been lacking.

Whereas the vast majority of publications in neuroimaging relate to structural and functional alterations of individual structures, there has been limited analysis of how these structures are organized as altered networks within the brain of persons with ADHD. The neural sys-

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

Accessible online at:
www.karger.com/dne

Nikos Makris, MD, PhD
Center for Morphometric Analysis, Massachusetts General Hospital
149 13th Street
Charlestown, MA 02129 (USA)
Tel. +1 617 726 5733, Fax +1 617 726 5677, E-Mail nikos@cma.mgh.harvard.edu

tems organization approach addresses at least 3 questions. The most basic of these questions is whether the structures shown to be altered in ADHD are indeed component parts of well-understood neural systems. Another critical question is whether these structural neural systems correlate with specific behaviors. Thirdly, a key question pertains as to whether these neural systems are associated with specific genotypes.

Historical Background of Brain Dysfunction Hypotheses in ADHD

ADHD was first described more than 100 years ago under the name 'hyperactivity' or 'hyperkinesis disorder in childhood' found mainly in boys [6]. In the 1960s it was renamed with the now outmoded terms 'minimal brain damage' or 'minimal brain dysfunction' suggesting that this could be a brain disorder. However, it was actually in the 1970s that neuropsychological studies of ADHD sparked a renaissance of interest in this childhood-onset malady when the feature of inattention was first introduced as its central defining feature [7]. The work of Douglas [7] demonstrated deficits on sustained attention tasks, such as the continuous performance test, replicated many times subsequently [8]. The renaming of the disorder and the focus on 'attention' led to a more focused analysis of the brain localization of attention deficits [9, 10], a drive catalyzed by novel insights in the neurological bases of attention [11–14]. This conceptual evolution led to an ever increasing number of studies over the past 2–3 decades designed to elucidate the brain basis of ADHD.

Symptom Basis for ADHD and Early Brain Localization Models

The diagnosis of ADHD is formulated upon developmentally inappropriate symptoms of inattention, impulsivity and motor restlessness, which are discernible before age 7 years, pervasive across situations and persistent to a large extent throughout adolescence and adulthood [5, 15]. The similarities that ADHD bears with certain neurological patients, have led to the hypothesis that ADHD is a brain disorder affecting the prefrontal cortex [10]. Based on the success of stimulant medications in humans and animal experimentation, the 'frontostriatal' model implicating dopamine pathways [16] suggested that amelioration of dopaminergic and noradrenergic functions is necessary for the clinical efficacy of pharmacologic treatment of ADHD [17]. Current insights emphasize the role of attentional and executive function (EF) difficulties in this disorder [18–20]. Although its etiology remains unclear, its strong familial nature [21, 22] and high levels of heritability (0.77) [23] strongly support a genetic etiology. The broad outlines of the etiology and pathophysiology of ADHD are depicted in figure 1.

Our understanding of the neuroanatomy of ADHD stems from the conceptualization of ADHD as a brain disorder of multifactorial etiology. ADHD is hypothesized to be a result of genetic and perinatal environmental factors whose effects unfold across development. The resulting pathophysiology is marked by dopaminergic and noradrenergic dysregulation, as well as structural and functional abnormalities in cortico-cortical and fronto-subcortical pathways [5], including the striatum and cerebellum. The evidence supporting this model of ADHD is strong as there are well-developed biological mechanisms that explain how they putatively cause ADHD (fig. 1). It should also be noted that, because this empirical pathway is derived from studies largely comprised of male subjects, the neuropathophysiology of ADHD in females remains less well known.

As described by Seidman et al. [24] and Valera et al. [25], the overwhelming majority of MRI studies of ADHD have been based almost solely on pediatric studies of boys with the disorder. While it is clear that putative biological risk factors are operant in the development of ADHD in females, uncertainties remain regarding how these factors express themselves through abnormal neuroanatomy, and, if they do, how that profile may deviate from non-ADHD females or males with the disorder.

Structural and Functional Neuroimaging in ADHD

Overview

Because to our knowledge there are no published traditional histopathological studies on ADHD [26], neuroimaging studies are key contributors to gaining insight into the neural bases of ADHD in humans. Structural imaging methods have localized abnormalities in key brain regions and neural networks associated with cognition and behavior consistent with the clinical picture of ADHD [24, 25]. Similarly, functional neuroimaging studies have shown functional differences in the same regions [27].

The neuroanatomy of ADHD is being actively investigated in many laboratories around the world, including

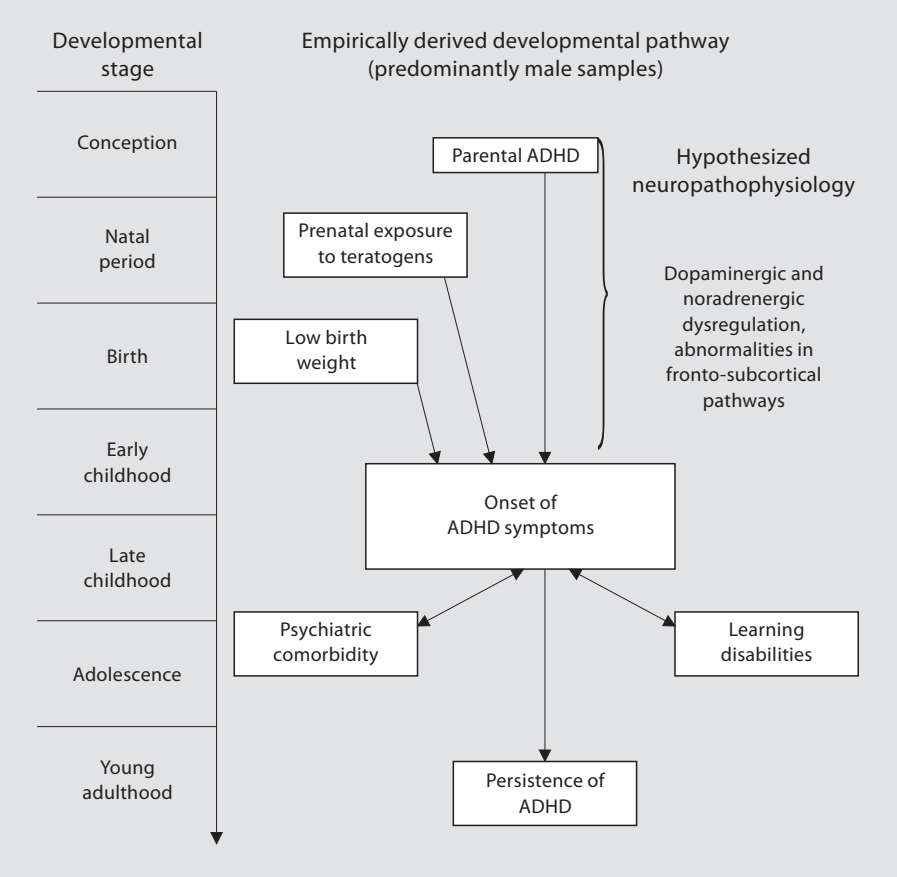

Fig. 1. Conceptual framework of the pathophysiology and etiology of ADHD.

ours. Convergent data from neuroimaging, neuropsychological, genetic and neurochemical studies have implicated dysfunction of dorsolateral prefrontal cortex (DLPFC) and dorsal anterior cingulate cortex (dACC) [20, 24, 27–32], which constitute the cortical arm of the frontostriatal network supporting EF. In addition to DLPFC and dACC, other regions within a distributed cortical network supporting attention have been identified including the posterior parietal cortex and centers at the temporo-occipito-parietal junction in the lateral surface of the right hemisphere, primarily the angular (Brodmann area, BA, 39) and supramarginal (BA 40) gyri [11, 13, 14, 33–36].

A growing literature of magnetic resonance imaging (MRI)-based volumetric [25, 37] and cortical thickness [38] studies have identified abnormalities in the DLPFC, the fronto-orbital cortex (FOC), the anterior cingulate cortex (ACC), the inferior parietal lobule and the corticostriatal system, which are structures subserving attention and EF.

Prefrontal Cortex

Prefrontal hypotheses of ADHD have principally implicated the DLPFC and FOC cortices. DLPFC lesions are associated with organizational, planning, working memory and other executive dysfunctions, whereas FOC lesions are related to reward behavior, social disinhibition and impulse dyscontrol. Given the persistence of EF deficits in adults with ADHD, the DLPFC is likely affected. Furthermore, behavioral inhibition is thought to be a core deficit in ADHD, which is related primarily to orbital frontal dysfunction [9].

Dorsal Anterior Cingulate Cortex

Another relevant cortical structure in ADHD is the dACC, which is currently considered to have a role in cognition and motor control, and to be involved in processes underlying the arousal/drive state of the organism [39, 40]. The dACC plays a role in complex cognitive operations [41] such as target detection, response selection, error detection, action monitoring and reward-based decision-making [42–47], functions that are thought to be

impaired in ADHD. Functional neuroimaging reports on normal subjects have shown that cognitive interference tasks such as the Stroop and Stroop-like tasks activate the dACC [48]. Furthermore, the dACC has been shown to be functionally abnormal in adults with ADHD using the counting Stroop task [28], a continuous performance test [49] and response inhibition tasks [50, 51]. In addition, to functional MRI abnormalities in the ACC, it has been shown that adults with ADHD have a smaller ACC volume than controls [35], and that the ACC in ADHD is significantly thinner than in matched controls [36]. Moreover, 2 studies showed volumetric decreases on the right ACC in treatment-naïve children with ADHD relative to treated children with ADHD and controls [52, 53].

Inferior Parietal Cortex

The inferior parietal lobule is a multimodal association area related to cognitive functions such as attention and language [11, 54–69]. Humans with damage in the right caudal inferior parietal area, i.e. the angular gyrus (BA 39), usually exhibit severe impairment in spatial attention referred to as hemi-inattention [65, 67, 70, 71], which is also one of the major behavioral manifestations of the neglect syndrome [71]. Alternatively, humans with lesions in the left angular gyrus usually show some type of language impairment [55, 56, 59, 60, 62, 63]. Commonly, these manifestations are associated with right-handedness in humans [61, 72]. Through its connections, the angular gyrus provides the prefrontal cortex with information concerning the perception of the visual space as well as linguistic information. Similarly, the prefrontal cortex via bidirectional connections directed back to the posterior parietal region could provide a means by which it can regulate the focusing of attention in different parts of space. Sowell et al. [31] reported an increased size of cortex in the inferior parietal lobule of children and adolescents with ADHD. This finding contrasts somewhat with the results of another study, which showed a decrease in cortical thickness of that region in adults with ADHD [38]. However, volumetric and cortical thickness measures are distinct measures and may not correlate with one another, and Sowell et al. [31] did not specifically report cortical thickness measures.

Corpus Striatum

The caudate, nucleus accumbens, putamen and globus pallidus are part of discrete distributed networks vital for executive functions. These networks include prefrontal/basal ganglia/thalamic loops [73]. Damage to the corpus striatum is plausibly associated with the etiology of ADHD [74]. Given its anatomic location at a border zone of arterial supply and its exposure to circulatory compromise, the striatum is vulnerable to perinatal hypoxic complications (which occur at higher than normal rates in ADHD) [75]. Experimental lesions in the striatum of animals produce hyperactivity and decreased performance in working memory and response inhibition tasks [73]. Moreover, the corpus striatum is one of the important sources of dopaminergic synapses [76], and dopamine is relevant in the regulation of striatal functions. Finally, stimulant medications, usually employed to treat ADHD, have been shown to have effects on the corpus striatum [77, 78]. A growing body of brain-imaging investigations supports a role for the basal ganglia in ADHD. Most studies have shown significantly smaller total caudate or smaller caudate head, either on the left or right side [29, 79–85]. Studies in children with ADHD have shown the globus pallidus to be smaller on the right [80, 86] or the left [29, 81, 87]. Furthermore, Castellanos et al. [29] demonstrated that significant differences between children with ADHD and controls in caudate volume diminished by the oldest age studied (19 years), thus showing a 'normalization' of brain volume over time. This suggests that studies of adults will be necessary to assess the persistence and stability of different anatomical changes in ADHD across the lifespan. Recently, Seidman et al. [37] showed in a preliminary study of the nucleus accumbens that it is larger in adults with ADHD. Given the role of this structure in emotional and autonomic control, its volumetric alteration may be related to reward dysregulation as well as impulsivity present in subjects with ADHD. Moreover, bilateral caudate volumetric decrease has been shown in treatment-naïve children with ADHD relative to treated children with ADHD and controls [53].

Cerebellum

The cerebellum has also been shown by several groups to be structurally altered in ADHD. Specifically, volumetric reductions in lobules VIII, IX and X of the vermis have been observed in both ADHD boys [80, 88–91] and girls [81, 90]. Bussing et al. [89] also found reductions in vermal lobules VI and VII. Furthermore, Castellanos et al. [29] found reductions in ADHD for all brain regions measured in a large group of 152 ADHD children and adolescents compared to 139 matched control subjects. However, when they adjusted for total cerebral volume, only the cerebellar volume differences remained significant, which also correlated significantly and negatively

with measures of attentional problems. Durston et al. [92] have corroborated the finding of a smaller cerebellum in a group of 30 ADHD children.

White Matter

The presence of this array of abnormalities in the DLPFC, dACC, inferior parietal cortex, corpus striatum and cerebellum, and possibly FOC, raises a critical question as to whether ADHD is a syndrome that may also involve disordered white matter (WM) connections linking these structures. Indeed, there is currently evidence from MRI structural investigations that WM alterations are present in children, adolescents and adults with ADHD [29, 37, 82, 86, 93, 94]. However, results are inconsistent so far. Whereas the studies conducted in children and adolescents with ADHD showed a reduction in overall WM volume [29], in adults with ADHD there was a trend toward an overall increase in WM volume [37]. Furthermore, these studies considered the cerebral WM in its entirety without investigating specific fiber pathways or adopting a neural systems perspective. There is only 1 published study using diffusion tensor MRI (DT-MRI) in children and adolescents with ADHD in which Ashtari et al. [95] conducted an investigation of a number of WM structural regions of interest, and found abnormalities within premotor, parieto-occipital, striatal and cerebellar regions. Another study using DT-MRI, conducted in adults with ADHD, addressed the issue of neural systems alterations in this subjects' population and demonstrated abnormalities in such fiber pathways as the superior longitudinal fascicle II and the cingulum bundle, which are affiliated with the attention and EF systems [96]. Whereas there is paucity of DT-MRI studies in ADHD, several investigations showing abnormalities of the corpus callosum have been reported in a number of morphometric studies of children with ADHD [85, 90, 97–100]. In these studies, different morphometric measures were used: some studies used 5 subdivisions following the O'Kusky method [101]; others instead used the 7 subdivisions in the approach of Witelson [102], making the results difficult to compare. Nevertheless, fairly consistent results indicate that abnormalities in children with ADHD are localized particularly in the posterior regions linked to temporal and parietal cortices at the region of the callosal isthmus and splenium [82, 85, 90, 99].

In addition to the structures mentioned earlier, for which there is a convergence from different published studies, it has also been shown that other brain regions, such as the right posterior cingulate volume, are reduced in children with ADHD [86],and also that in children and adolescents with ADHD the hippocampus is enlarged bilaterally [103]. The relevance of these findings is not yet clearly understood, and future studies need to add insight regarding their meaning in the disorder.

Developmental Considerations

Recently, Shaw et al. [104] addressed the question of whether ADHD is associated with a delay in typical brain maturation or a 'complete deviation from the template of typical development'. This study examined a sample of 223 children with ADHD and 223 controls, and used the age of attaining peak cortical thickness as a measure of cortical maturation. There was a significant difference in the median age by which 50% of the cortical points attained peak thickness in the ADHD group compared to the controls (10.5 years and 7.5 years, respectively). This delayed effect was strongest in prefrontal regions. Despite the elegance of this work, it only covered brain development until the age of 20 years. Since considerable brain development continues to occur beyond age 20 years, this work currently cannot answer the question as to the persistence of delayed maturation or dysmaturations into adult life. One sense of the term 'delay' implies a transient phase of slowed development followed by 'catching up' to normal development. If such catching-up occurs, then at some point in adult life, persons with ADHD ought to have brain structures not significantly different than healthy controls. Another perspective on this question more generally was asked by Sowell et al. [31]: 'At what age during the human life span do different tissues stop "maturing" and start "aging"?' [31]. The answer to this latter question appears to be, on the one hand, that cortical change continues to occur across the life span, and that the developmental trajectories of change vary across structure and tissue types. On the other hand, certain gray matter structures, i.e. the late developing cortical structures, such as the DLPFC and posterior temporal regions, reach largely or completely mature levels by the mid-20s or 30 years of age. Furthermore, WM development continues in a linear way into the fourth or fifth decade of life [105]. Our own data thus far on adults averaging about age 35 is that persistent cases retain structural alterations in the prefrontal cortex, dACC, inferior parietal lobule and cerebellum [37, 38], but this requires further replication as these studies thus far are comprised of small samples.

Neural Systems' Neuroanatomy in ADHD

ADHD has been hypothesized to be due, in part, to structural defects in brain networks influencing cognitive and motor behavior [9, 38, 106]. Neural networks are dedicated to the performance of specific functions, and are assemblies of centers and the fiber tracts that interconnect them. In the central nervous system, besides perception and motor activity, which principally engage the primary cortices and the thalamus, a set of emotional and higher brain functions are affiliated with the multimodal associative cortical areas as well as subcortical centers. The latter can be cognitive functions, such as executive, working memory, attention and language, or affective behaviors such as fear, happiness, impulsivity and sadness.

Defining ADHD-Relevant Neural Networks

Below we describe a series of networks, including assemblies of gray matter structures and the fiber tracts that connect them, in the healthy brain. We focus on specific networks that are hypothesized to be impaired in ADHD, based in part on the literature we reviewed above, and linked to ADHD symptoms (fig. 2). The functional neuroanatomy described below is organized by function (attention, EF, etc.).

Attention. The core of the attention network includes the lateral and medial prefrontal cortices, the lateral-inferior parietal and temporo-occipito-parietal cortices in the surface of the right hemisphere [12, 14, 34, 71, 107, 108] (i.e. middle and superior lateral frontal gyri, the inferior parietal lobule including the angular and supramarginal gyri and the cingulate gyrus [11, 13, 14, 33–36, 57]). The principal connecting fiber pathways are 3 subcomponents of the superior longitudinal fascicle (I, II and III), the cingulum bundle (CB) and the inferior longitudinal fascicle [109–117]. The splenium and the isthmus of the corpus callosum, involved in the transfer of information across the hemispheres to parietal, temporal and occipital areas [118] and thalamic nuclei (including medial dorsal, reticular and pulvinar), are both involved in attention, including sensory gating.

Executive Functions. EF allow a person to formulate goals and goal-directed plans and to carry them out effectively [35, 36, 107, 119]. The EF circuitry principally involves prefrontal cortical and striatal regions [120–124], as well as cortical limbic structures such as the ACC [28, 51, 125]. Due to its connections, the ACC is critical for monitoring, balancing and deciding how and when to allocate cognitive control [40, 42–47]. The principal fiber tracts mediating these connections are the CB and the corticostriatal projection bilaterally [111, 114]. EF deficits are well documented in ADHD [18, 126].

Motor Regulation (Cortico-Striatal and Cortico-Cerebellar) Circuitry. This network consists of parallel circuits that subserve motor, cognitive and emotional behaviors. Makris et al. [127] proposed a mapping framework of the cortico-striatal system, within which caudate and putamen are complementary targets of the neocortical to striatal projection [128–144]. The caudate receives projections from the extrastriate, lateral parietal and lateral frontal areas, the mesial hemispheric surface and the temporal cortices. The cortico-pallidal projections are from premotor and from primary somatosensory and motor cortices [133, 134]. The fronto-cerebellar circuit connects the frontal-cortical regions with the cerebellum, in a loop. The cerebellar contribution to the organization of higher order brain functions has been recently shown, including in ADHD [145–152]. The cerebellum is topologically linked to different cerebral primary sensorimotor and association areas through the pons via the feed-forward pathway, and by way of the thalamus via the feedback pathway [149, 150, 152–154]. Motor deficits are characteristic of ADHD such as moving or talking excessively in inappropriate situations and poor fine motor ability [155] as well as timing and force control [156].

Reward. This circuitry consists principally of the amygdala, nucleus accumbens septi, basal forebrain (including the sublenticular extended amygdala), striatum, thalamus, limbic brainstem and cortical areas such as the fronto-orbital, ACC, anterior insula and DLPFC [157–165]. The reward system is central to memory consolidation and recall, spatial and contextual sensory processing, integrating stimulus reward associations, reward guided behaviors and determining mood. Reward dysfunctions are hypothesized to be important in ADHD [166].

Emotion Regulation. This network involves the amygdala, fronto-orbital cortex, pregenual cingulate and the cerebellar vermis. The fiber tracts involved are the CB and the amygdalofugal pathway. The cerebellar vermis is connected via corticopontine and pontocerebellar fibers and the cerebello-thalamo-cortical loop to the cortical centers. These circuits may be abnormal in persons with ADHD who have excessive irritability, and especially those with mood instability.

Mapping Abnormal Networks in ADHD. The proposed neural networks derive from neuroimaging studies of ADHD primarily in male children [25, 167], work with adults [37, 38], and the functional neuroanatomy of symptoms and neurocognitive deficits associated with the dis-

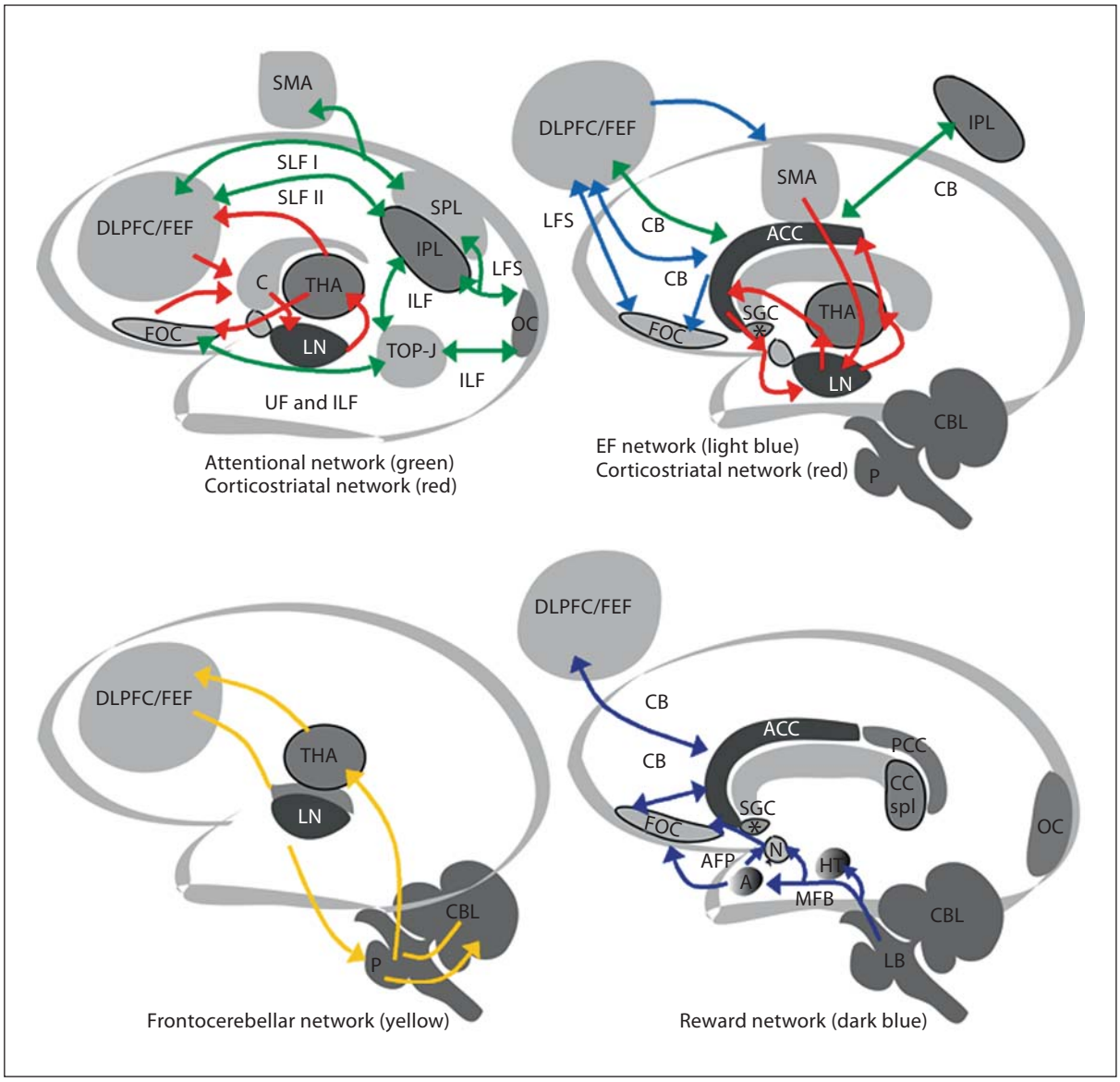

Fig. 2. Functional neuroanatomy of circuits involved in the pathophysiology of ADHD. A = Amygdala; ACC = anterior cingulate cortex; AFP = amygdalofugal pathway; C = caudate nucleus; CBL = cerebellum; Ccspl = splenium of corpus callosum (including isthmus); FEF = frontal eye field; HT = hypothalamus; ILF = inferior longitudinal fascicle; IPL = inferior parietal lobule; LB = limbic brainstem; LFS = local fiber system; LN = lenticular nucleus; MFB = medial forebrain bundle; N = nucleus accumbens; OC = occipital cortex; P = pons; PCC = posterior cingulate cortex; SGC = subgenual cingulate cortex; SLF = superior longitudinal fascicle; SMA = supplementary motor area; SPL = superior parietal lobule; THA = thalamus; TOP = temporo-occipito-parietal junction; UF = uncinate fascicle.

order [8] (fig. 3). The mapping of ADHD abnormalities in these structural and functional networks is organized around dysfunctions in key structures (i.e. dACC), coordinated functional neural networks (e.g. DLPFC and inferior parietal lobule for working memory) and structural networks (i.e. DLPFC, dACC and the CB for attention). Our organizing framework is that behavioral symptoms and cognitive deficits in ADHD arise from damage or dysfunction in these networks as well as compensation by other networks. The ACC has attracted considerable attention as one of the principal structures implicated in ADHD [28, 37, 51]. Failure of ACC connections with oth-

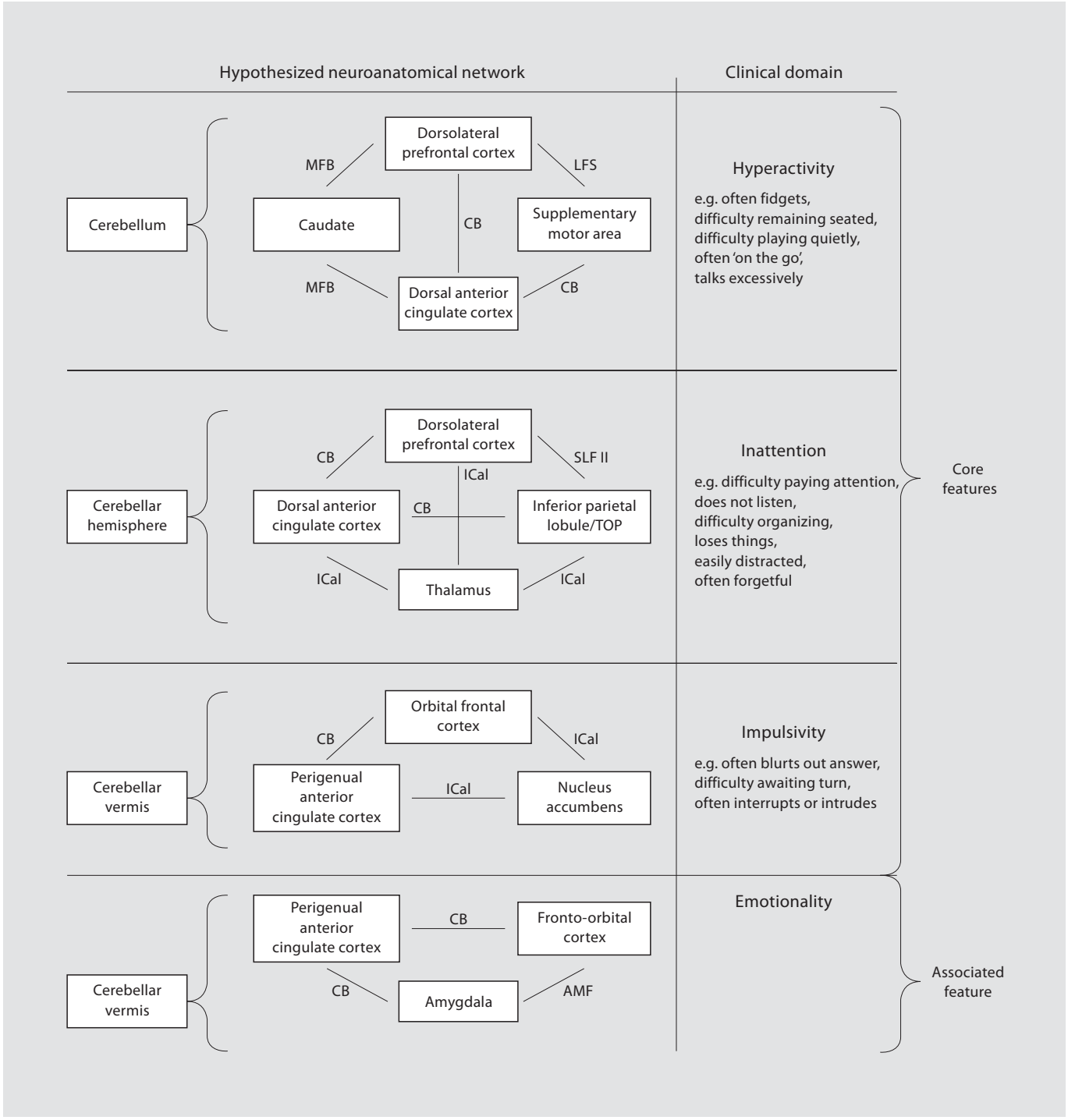

Fig. 3. Conceptual model of the neuroanatomical substrates of ADHD. AMF = Amygdalo-fugal pathway; MFB = medial forebrain bundle; LFS = local fiber system; SLF II = superior longitudinal fascicle; ICal = internal capsule anterior limb; TOP = temporo-occipito-parietal junction.

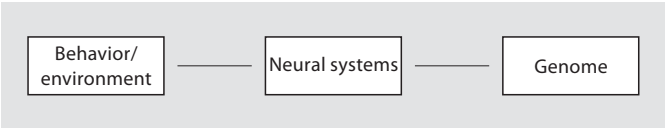

Fig. 4. Neural systems biology acts as an interface between behavior and the genome.

er cortical and subcortical centers may result in a disturbance of fundamental cortical properties that underlie ADHD symptoms. Likewise, the reward system may be strongly involved in many functions impaired in ADHD subjects and its breakdown or dysfunction may be critical for a variety of behavioral abnormalities. The reward-aversion circuitry may be an integral part of the neurobiology of ADHD, as it is thought to be for other conditions such as drug addiction, and particularly involved in all sources of reinforcement. Evidence suggests that when the mesocorticolimbic system malfunctions there is a high risk of the appearance of drug-seeking behaviors and 'reward deficiency syndrome' [158, 168]. The mesocorticolimbic system is a complex and interrelated network with many functions, including sensitivity to the actions of positive and negative reinforcement [158, 169]. We posit that in ADHD, alterations in the cortico-striatial circuitry could produce deficits in motor control such as moving (running, climbing, fidgeting with hands or feet, etc.) excessively in inappropriate situations or talking excessively. These deficits in motor regulation could be accentuated with abnormalities in the cortico-cerebellar circuitry. Furthermore, alterations in the fronto-cerebellar network could decrease the efficiency of EF [149].

Studying Neural Systems as Endophenotypes in ADHD

The demonstration that ADHD is a neurobiological disorder fueled interest in the basic brain properties that might mediate its phenotypic expression. Consequently there has been a focus on the brain structures related to these behavioral correlates as well as the neural networks in which these structures are assembled. The genotype-phenotype paradigm aims to identify causal relationships between biological markers and the genes [159, 170, 171].

Currently, neuroimaging has allowed the characterization of brain structure in an unprecedented way using different imaging modalities such as T_1-weighted MRI, DT-MRI and fMRI [134]. Once we quantify imaging-based markers, i.e. endophenotypes, we will be able to diagnose ADHD, assess its treatment and identify genes that may lead to novel medications. Studying multiple anatomical regions that are components of a structural and functional circuit may be an important avenue to identify biomarkers for a disease. According to this view, systems biology acts as an interface between the behavior and the genome (fig. 4) [159, 172]. In ADHD, the neural networks subserving attention, EF and impulsivity are putative biomarkers of the disorder. Thus, their structural quantification using MRI may ultimately be relevant for diagnostic and therapeutic purposes in ADHD.

ADHD can be conceptualized as a multisystem developmental disorder that has variable clinical expression, based in part on the heterogeneity and degree of neural systems dysfunction. Different neural systems can be affected due to genetic heterogeneity, genetic and environment interaction (i.e. influence of certain environmental events such as maternal smoking and alcohol use on brain development), the timing of occurrence of these events, i.e. when in pregnancy, and the severity of the insult. Genetic heterogeneity could lead to phenotypic variation that can be observed in the endophenotype measured by neuroimaging techniques. The concept of a multisystem disorder suggests variation in pathology ranging from relatively focal dysfunction to a large range of abnormalities that is organized along domains of neural systems and behavior. This differs from the concept of a diffuse disorder, in which widespread pathology is suggested.

Durston et al. [173] provide an example of how complex genetic influences may selectively influence brain structure, and suggest that this approach has much potential for the future. They showed a dissociation between the effects of 2 dopamine genes that are linked to ADHD (*DAT1* and *DRD4*), and are expressed in the brain selectively (basal ganglia and prefrontal cortex, respectively). In their study of subjects with ADHD, unaffected siblings and healthy controls, the *DAT1* gene largely influenced caudate volume, whereas the *DRD4* gene was mainly associated with prefrontal gray matter volume [173]. This study supports the idea of using intermediate phenotypes, such as those derived from neuroimaging, to identify the pathways by which genes influence brain structure in a disorder like ADHD. Future work could study the gene-environment interaction in such a design by adding perinatal risk factors, such as maternal smoking (another risk factor for ADHD), to determine the separate and potentially interactive effects on brain structure and behavior.

Summary

Our review suggests that there is substantial support for the hypothesis indicating a critical brain abnormality in ADHD involving structural and functional alterations in the fronto-subcortical circuitry, although this has been broadened to include posterior cortical areas and the cerebellum [174, 175]. This extension of circuitry abnormalities is based on the growing evidence that other brain regions, such as the inferior parietal lobule and the cerebellar vermis, are also altered in ADHD. It has to be noted that there is a high degree of variation among the different studies regarding the probable influence of therapeutic interventions, comorbidities, age and gender. In addition, other potential sources of heterogeneity, such as variability in family history of ADHD and perinatal complications, have been poorly addressed in the extant literature. Despite these limitations there is a relatively consistent pattern of structural alterations in ADHD to date [25, 29, 104]. In children with ADHD, the most replicated abnormalities include smaller DLPFC, caudate, pallidum, corpus callosum and cerebellum. Although findings of smaller total brain volumes and widespread cortical changes, derived by region-of-interest-based techniques [29] and automated procedures [31], indicate that the brain may be altered in a more diffuse manner, specific structural alterations of neural systems [38, 96] suggest that there may be more circumscribed and organized brain phenotypes in ADHD.

The conceptualization of neural systems biology in ADHD is a step towards the understanding of what organizing principles have been altered during development within the brain of a subject with ADHD. Furthermore, the identification of these neural systems is critical for the characterization of brain abnormalities and structural endophenotypes detectable by neuroimaging. Moreover, the quantification of neural systems using imaging provides the capability of in vivo categorization and correlation with behavior and genes. These capabilities will add greater knowledge and will help clarify the etiology of the disorder, its neurodevelopmental course, its response to treatment and the meaning of ADHD to patients, their families and treating clinicians.

Acknowledgments

This work was primarily supported by a grant from the National Institutes of Mental Health, No. MH 62152 (L.J.S.). Preparation of this article was also supported in part by grants from: The National Association for Research in Schizophrenia and Depression and the National Institutes of Health National Center for Complementary and Alternative Medicine, No. PO1AT002048-05 (N.M.); the National Alliance for Research on Schizophrenia and Depression Distinguished Investigator Award (J.B.), Janssen Pharmaceuticals and the Johnson and Johnson Center for the Study of Psychopathology (J.B.); the Fairway Trust (D.K.); The National Center for Research Resources, No. P41RR14075; the March of Dimes Foundation (L.J.S.), and the Mental Illness and Neuroscience Discovery Institute (L.J.S.).

J.B. is currently receiving research support from the following sources: Bristol Myers Squibb, Eli Lilly and Co., Janssen Pharmaceuticals, McNeil, Otsuka, Shire, NIMH, and NICHD. J.B. is currently a consultant/advisory board member for the following pharmaceutical companies: Janssen, McNeil, Novartis and Shire. J.B. is currently a speaker for the following speakers' bureaus: Janssen, McNeil, Novartis, Shire and UCB Pharma. In previous years, J.B. received research support, consultation fees or speaker's fees for/from the following additional sources: Abbott, AstraZeneca, Celltech, Cephalon, Eli Lilly and Co., Esai, Forest, Glaxo, Gliatech, NARSAD, New River, NIDA, Novartis, Noven, Neurosearch, Pfizer, Pharmacia, The Prechter Foundation, The Stanley Foundation and Wyeth. M.C.M. has participated in a symposium funded by Shire.

The authors gratefully acknowledge Dr. Eve Valera and Mr. Jonathan Kaiser for their valuable contributions to the preparation of this manuscript.

References

1 Kessler RC, Adler LA, Barkley R, Biederman J, Conners CK, Faraone SV, Greenhill LL, Jaeger S, Secnik K, Spencer T, Ustun TB, Zaslavsky AM: Patterns and predictors of attention-deficit/hyperactivity disorder persistence into adulthood: results from the national comorbidity survey replication. Biol Psychiatry 2005;57:1442–1451.

2 Faraone SV, Sergeant J, Gillberg C, Biederman J: The worldwide prevalence of ADHD: is it an American condition? World Psychiatry 2003;2:104–113.

3 Faraone SV, Biederman J: Prevalence of Adult ADHD in the United States. Washington, APA, 2004.

4 Kessler RC, Merikangas KR: The National Comorbidity Survey Replication (NCS-R): background and aims. Int J Methods Psychiatr Res 2004;13:60–68.

5 Biederman J: Attention-deficit/hyperactivity disorder: a selective overview. Biol Psychiatry 2005;57:1215–1220.

6 Still G: The Goulstonian lectures on some abnormal physical conditions in children. Lecture 1. Lancet 1902;i:1008–0102, 1077–1082, 1163–1168.

7 Douglas VI: Stop, look and listen: the problem of sustained attention and impulse control in hyperactive and normal children. Can J Behav Sci 1972;4:259–282.

8 Seidman LJ: Neuropsychological functioning in people with ADHD across the lifespan. Clin Psychol Rev 2006;26:466–485.

9 Barkley RA: Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychol Bull 1997;121:65–94.
10 Mattes JA: The role of frontal lobe dysfunction in childhood hyperkinesis. Compr Psychiatry 1980;21:358–369.
11 Heilman KM, Pandya DN, Geschwind N: Trimodal inattention following parietal lobe ablations. Trans Am Neurol Assoc 1970;95: 259–261.
12 Heilman KM, Watson RT, Bower D, Valenstein E: Right hemisphere dominance for attention (in French). Rev Neurol (Paris) 1983; 139:15–17.
13 Mesulam MM: Large-scale neurocognitive networks and distributed processing for attention, language, and memory. Ann Neurol 1990;28:597–613.
14 Posner MI, Petersen SE: The attention system of the human brain. Annu Rev Neurosci 1990;13:25–42.
15 American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, ed 4. Washington, American Psychiatric Association, 1994.
16 Shaywitz BA, Klopper JH, Gordon JW: Methylphenidate in 6-hydroxydopamine-treated developing rat pups: effects on activity and maze performance. Arch Neurol 1978;35: 463–469.
17 Elia J, Borcherding BG, Potter WZ, Mefford IN, Rapoport JL, Keysor CS: Stimulant drug treatment of hyperactivity: biochemical correlates. Clin Pharmacol Ther 1990;48:57–66.
18 Pennington BF, Ozonoff S: Executive functions and developmental psychopathology. J Child Psychol Psychiatry 1996;37:51–87.
19 Seidman LJ, Doyle A, Fried R, Valera E, Crum K, Matthews L: Neuropsychological function in adults with attention-deficit/hyperactivity disorder. Psychiatr Clin North Am 2004;27:261–282.
20 Seidman LJ, Valera EM, Bush G: Brain function and structure in adults with attention-deficit/hyperactivity disorder. Psychiatr Clin North Am 2004;27:323–347.
21 Faraone SV, Doyle AE: The nature and heritability of attention-deficit/hyperactivity disorder. Child Adolesc Psychiatr Clin N Am 2001;10:299–316, viii–ix.
22 Faraone SV, Tsuang MT: Methods in psychiatric genetics; in Tohen M, Tsuang MT, Zahner GEP (eds): Textbook in Psychiatric Epidemiology. New York, John Wiley, 1995, pp 81–134.
23 Faraone SV: The scientific foundation for understanding attention-deficit/hyperactivity disorder as a valid psychiatric disorder. Eur Child Adolesc Psychiatry 2005;14:1–10.
24 Seidman LJ, Valera EM, Makris N: Structural brain imaging of attention-deficit/hyperactivity disorder. Biol Psychiatry 2005;57: 1263–1272.
25 Valera EM, Faraone SV, Murray KE, Seidman LJ: Meta-analysis of structural imaging findings in attention-deficit/hyperactivity disorder. Biol Psychiatry 2007;61:1361–1369.
26 Duane DD: Neurobiological correlates of learning disabilities. J Am Acad Child Adolesc Psychiatry 1989;28:314–318.
27 Bush G, Valera EM, Seidman LJ: Functional neuroimaging of attention-deficit/hyperactivity disorder: a review and suggested future directions. Biol Psychiatry 2005;57:1273–1284.
28 Bush G, Frazier JA, Rauch SL, Seidman LJ, Whalen PJ, Jenike MA, Rosen BR, Biederman J: Anterior cingulate cortex dysfunction in attention-deficit/hyperactivity disorder revealed by fMRI and the counting Stroop. Biol Psychiatry 1999;45:1542–1552.
29 Castellanos FX, Lee PP, Sharp W, Jeffries NO, Greenstein DK, Clasen LS, Blumenthal JD, James RS, Ebens CL, Walter JM, Zijdenbos A, Evans AC, Giedd JN, Rapoport JL: Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. JAMA 2002;288:1740–1748.
30 Durston S: A review of the biological bases of ADHD: what have we learned from imaging studies? Ment Retard Dev Disabil Res Rev 2003;9:184–195.
31 Sowell ER, Thompson PM, Welcome SE, Henkenius AL, Toga AW, Peterson BS: Cortical abnormalities in children and adolescents with attention-deficit hyperactivity disorder. Lancet 2003;362:1699–1707.
32 Kieling C, Goncalves RR, Tannock R, Castellanos FX: Neurobiology of attention deficit hyperactivity disorder. Child Adolesc Psychiatr Clin N Am 2008;17:285–307.
33 Cabeza R, Nyberg L: Neural bases of learning and memory: functional neuroimaging evidence. Curr Opin Neurol 2000;13:415–421.
34 Corbetta M, Shulman GL: Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 2002;3:201–215.
35 Duncan J, Owen AM: Common regions of the human frontal lobe recruited by diverse cognitive demands. Trends Neurosci 2000; 23:475–483.
36 Goldman-Rakic PS: Topography of cognition: parallel distributed networks in primate association cortex. Annu Rev Neurosci 1988;11:137–156.
37 Seidman LJ, Valera EM, Makris N, Monuteaux MC, Boriel DL, Kelkar K, Kennedy DN, Caviness VS, Bush G, Aleardi M, Faraone SV, Biederman J: Dorsolateral prefrontal and anterior cingulate cortex volumetric abnormalities in adults with attention-deficit/hyperactivity disorder identified by magnetic resonance imaging. Biol Psychiatry 2006; 60:1071–1080.
38 Makris N, Biederman J, Valera EM, Bush G, Kaiser J, Kennedy DN, Caviness VS, Faraone SV, Seidman LJ: Cortical thinning of the attention and executive function networks in adults with attention-deficit/hyperactivity disorder. Cereb Cortex 2007;17:1364–1375.
39 Dum R, Strick P: Cingulate motor areas; in Vogt BA, Gabriel M (eds): Neurobiology of Cingulate Cortex and Limbic Thalamus: A Comprehensive Handbook. Boston, Birkhauser, 1993.
40 Paus T: Primate anterior cingulate cortex: where motor control, drive and cognition interface. Nat Rev Neurosci 2001;2:417–424.
41 Bush G, Luu P, Posner MI: Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn Sci 2000;4:215–222.
42 Botvinick M, Nystrom LE, Fissell K, Carter CS, Cohen JD: Conflict monitoring versus selection-for-action in anterior cingulate cortex. Nature 1999;402:179–181.
43 Bush G, Vogt BA, Holmes J, Dale AM, Greve D, Jenike MA, Rosen BR: Dorsal anterior cingulate cortex: a role in reward-based decision making. Proc Natl Acad Sci USA 2002; 99:523–528.
44 Carter CS, Braver TS, Barch DM, Botvinick MM, Noll D, Cohen JD: Anterior cingulate cortex, error detection, and the online monitoring of performance. Science 1998;280: 747–749.
45 Carter CS, Macdonald AM, Botvinick M, Ross LL, Stenger VA, Noll D, Cohen JD: Parsing executive processes: strategic vs. evaluative functions of the anterior cingulate cortex. Proc Natl Acad Sci USA 2000;97: 1944–1948.
46 Cohen JD, Botvinick M, Carter CS: Anterior cingulate and prefrontal cortex: who's in control? Nat Neurosci 2000;3:421–423.
47 Gehring WJ, Knight RT: Prefrontal-cingulate interactions in action monitoring. Nat Neurosci 2000;3:516–520.
48 Paus T, Koski L, Caramanos Z, Westbury C: Regional differences in the effects of task difficulty and motor output on blood flow response in the human anterior cingulate cortex: a review of 107 PET activation studies. Neuroreport 1998;9:R37–R47.
49 Zametkin AJ, Nordahl TE, Gross M, King AC, Semple WE, Rumsey J, Hamburger S, Cohen RM: Cerebral glucose metabolism in adults with hyperactivity of childhood onset. N Engl J Med 1990;323:1361–1366.
50 Rubia K, Overmeyer S, Taylor E, Brammer M, Williams SC, Simmons A, Bullmore ET: Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control: a study with functional MRI. Am J Psychiatry 1999;156:891–896.
51 Tamm L, Menon V, Ringel J, Reiss AL: Event-related FMRI evidence of frontotemporal involvement in aberrant response inhibition and task switching in attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2004;43:1430–1440.

52 Pliszka SR, Glahn DC, Semrud-Clikeman M, Franklin C, Perez R 3rd, Xiong J, Liotti M: Neuroimaging of inhibitory control areas in children with attention deficit hyperactivity disorder who were treatment naive or in long-term treatment. Am J Psychiatry 2006; 163:1052–1060.
53 Semrud-Clikeman M, Pliszka SR, Lancaster J, Liotti M: Volumetric MRI differences in treatment-naive vs. chronically treated children with ADHD. Neurology 2006;67:1023–1027.
54 Brain W: Visual disorientation with special reference to lesions of the right cerebral hemisphere. Brain 1941;64:244–272.
55 Caplan D: Language: Structure, Processing and Disorders. Cambridge, MIT Press, 1992.
56 Caplan D, Evans KL: The effects of syntactic structure on discourse comprehension in patients with parsing impairments. Brain Lang 1990;39:206–234.
57 Critchley M: Is developmental dyslexia the expression of minor cerebral damage? Clin Proc Child Hosp Dist Columbia 1966;22: 213–222.
58 Denny-Brown D, Banker BQ: Amorphosynthesis from left parietal lesion. AMA Arch Neurol Psychiatry 1954;71:302–313.
59 Geschwind N: Disconnexion syndromes in animals and man. I. Brain 1965;88:237–294.
60 Geschwind N: Disconnexion syndromes in animals and man. II. Brain 1965;88:585–644.
61 Geschwind N, Galaburda AM: Cerebral lateralization: biological mechanisms, associations and pathology. Cambridge, MIT Press, 1987.
62 Geschwind N, Kaplan E: A human cerebral deconnection syndrome: a preliminary report. Neurology 1962;12:675–685.
63 Goodglass H, Wingfield A: Selective preservation of a lexical category in aphasia: dissociations in comprehension of body parts and geographical place names following focal brain lesion. Memory 1993;1:313–328.
64 McFie J, Piercy MF, Zangwill OL: Visual-spatial agnosia associated with lesions of the right cerebral hemisphere. Brain 1950;73: 167–190.
65 Mesulam MM: A cortical network for directed attention and unilateral neglect. Ann Neurol 1981;10:309–325.
66 Paterson A, Zangwill OL: Recovery of spatial orientation in the post-traumatic confusional state. Brain 1944;67:54–68.
67 Posner MI, Walker JA, Friedrich FJ, Rafal RD: Effects of parietal injury on covert orienting of attention. J Neurosci 1984;4:1863–1874.
68 Riddoch G: Visual disorientation in homonymous half-fields. Brain 1935;58:383–397.
69 Sperry R: Cerebral organization and behavior. Science 1961;133:1749–1757.
70 Heilman KM, Van Den Abell T: Right hemispheric dominance for mediating cerebral activation. Neuropsychologia 1979;17:315–321.
71 Heilman KM, Van Den Abell T: Right hemisphere dominance for attention: the mechanism underlying hemispheric asymmetries of inattention (neglect). Neurology 1980;30: 327–330.
72 Annett M: The binomial distribution of right, mixed and left handedness. Q J Exp Psychol 1967;19:327–333.
73 Alexander GE, DeLong MR, Strick PL: Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 1986;9:357–381.
74 Lou HC: Etiology and pathogenesis of attention-deficit hyperactivity disorder (ADHD): significance of prematurity and perinatal hypoxic-haemodynamic encephalopathy. Acta Paediatr 1996;85:1266–1271.
75 Sprich-Buckminster S, Biederman J, Milberger S, Faraone S, Krifcher Lehman B: Are perinatal complications relevant to the manifestation of ADD? Issues of comorbidity and familiality. J Am Acad Child Adolesc Psychiatry 1993;32:1032–1037.
76 Dougherty DD, Bonab AA, Spencer TJ, Rauch SL, Madras BK, Fischman AJ: Dopamine transporter density is elevated in patients with ADHD. Lancet 1999;354:2132–2133.
77 Solanto MV: Dopamine dysfunction in AD/HD: integrating clinical and basic neuroscience research. Behav Brain Res 2002;130:65–71.
78 Volkow ND, Fowler JS, Wang GJ, Ding YS, Gatley SJ: Role of dopamine in the therapeutic and reinforcing effects of methylphenidate in humans: results from imaging studies. Eur Neuropsychopharmacol 2002;12: 557–566.
79 Castellanos F, Giedd J, Eckburg P, Marsh W, Vaituzis C, Kaysen D, Hamburger S, Rapoport J: Quantitative morphology of the caudate nucleus in attention deficit hyperactivity disorder. Am J Psychiatry 1994;151: 1791–1796.
80 Castellanos F, Giedd J, Marsh W, Hamburger S, Vaituzis A, Dickstein D, Sarfatti S, Vauss Y, Snell J, Rajapakse J, Rapoport J: Quantitative brain magnetic resonance imaging in attention deficit hyperactivity disorder. Arch Gen Psychiatry 1996;53:607–616.
81 Castellanos FX, Giedd JN, Berquin PC, Walter JM, Sharp W, Tran T, Vaituzis AC, Blumenthal JD, Nelson J, Bastain TM, Zijdenbos A, Evans AC, Rapoport JL: Quantitative brain magnetic resonance imaging in girls with attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 2001;58:289–295.
82 Filipek PA, Semrud-Clikeman M, Steingard RJ, Renshaw PF, Kennedy DN, Biederman J: Volumetric MRI analysis comparing subjects having attention-deficit hyperactivity disorder with normal controls. Neurology 1997;48:589–601.
83 Hynd GW, Hern KL, Novey ES, Eliopulis D, Marshall R, Gonzalez JJ, Voeller KK: Attention deficit-hyperactivity disorder and asymmetry of the caudate nucleus. J Child Neurol 1993;8:339–347.
84 Mataro M, Garcia-Sanchez C, Junque C, Estevez-Gonzalez A, Pujol J: Magnetic resonance imaging measurement of the caudate nucleus in adolescents with attention-deficit hyperactivity disorder and its relationship with neuropsychological and behavioral measures. Arch Neurol 1997;54:963–968.
85 Semrud-Clikeman MS, Filipek PA, Biederman J, Steingard R, Kennedy D, Renshaw P, Bekken K: Attention-deficit hyperactivity disorder: magnetic resonance imaging morphometric analysis of the corpus callosum. J Am Acad Child Adolesc Psychiatry 1994;33: 875–881.
86 Overmeyer S, Bullmore ET, Suckling J, Simmons A, Williams SC, Santosh PJ, Taylor E: Distributed grey and white matter deficits in hyperkinetic disorder: MRI evidence for anatomical abnormality in an attentional network. Psychol Med 2001;31:1425–1435.
87 Aylward EH, Reiss AL, Reader MJ, Singer HS, Brown JE, Denckla MB: Basal ganglia volumes in children with attention-deficit hyperactivity disorder. J Child Neurology 1996;11:112–115.
88 Berquin PC, Giedd JN, Jacobsen LK, Hamburger SD, Krain AL, Rapoport JL, Castellanos FX: Cerebellum in attention-deficit hyperactivity disorder: a morphometric MRI study. Neurology 1998;50:1087–1093.
89 Bussing R, Grudnik J, Mason D, Wasiak M, Leonard C: ADHD and conduct disorder: an MRI study in a community sample. World J Biol Psychiatry 2002;3:216–220.
90 Hill DE, Yeo RA, Campbell RA, Hart B, Vigil J, Brooks W: Magnetic resonance imaging correlates of attention-deficit/hyperactivity disorder in children. Neuropsychology 2003; 17:496–506.
91 Mostofsky SH, Reiss AL, Lockhart P, Denckla MB: Evaluation of cerebellar size in attention-deficit hyperactivity disorder. J Child Neurol 1998;13:434–439.
92 Durston S, Hulshoff Pol HE, Schnack HG, Buitelaar JK, Steenhuis MP, Minderaa RB, Kahn RS, van Engeland H: Magnetic resonance imaging of boys with attention-deficit/hyperactivity disorder and their unaffected siblings. J Am Acad Child Adolesc Psychiatry 2004;43:332–340.
93 Hynd GW, Semrud-Clikeman MS, Lorys AR, Novey ES, Eliopulos D: Brain morphology in developmental dyslexia and attention deficit/hyperactivity. Arch Neurol 1990;47: 919–926.
94 Mostofsky S, Cooper K, Kates W, Denckla M, Kaufmann W: Smaller prefrontal and premotor volumes in boys with attention-deficit/hyperactivity disorder. Biol Psychiatry 2002;52:785.

95 Ashtari M, Kumra S, Bhaskar SL, Clarke T, Thaden E, Cervellione KL, Rhinewine J, Kane JM, Adesman A, Milanaik R, Maytal J, Diamond A, Szeszko P, Ardekani BA: Attention-deficit/hyperactivity disorder: a preliminary diffusion tensor imaging study. Biol Psychiatry 2005;57:448–455.
96 Makris N, Buka SL, Biederman J, Papadimitriou GM, Hodge SM, Valera EM, Brown AB, Bush G, Monuteaux MC, Caviness VS, Kennedy DN, Seidman LJ: Attention and executive systems abnormalities in adults with childhood ADHD: a DT-MRI study of connections. Cereb Cortex 2008;18:1210–1220.
97 Baumgardner TL, Singer HS, Denckla MB, Rubin MA, Abrams MT, Colli MJ, Reiss AL: Corpus callosum morphology in children with Tourette syndrome and attention deficit hyperactivity disorder. Neurology 1996;47:1–6.
98 Giedd JN, Castellanos FX, Casey BJ, Kozuch P, King AC, Hamburger SD, Rapoport JL: Quantitative morphology of the corpus callosum in attention deficit hyperactivity disorder. Am J Psychiatry 1994;151:665–669.
99 Hynd GW, Semrud-Clikeman M, Lorys AR, Novey ES, Eliopulos D, Lytinen H: Corpus callosum morphology in attention-deficit hyperactivity disorder: morphometric analysis of MRI. J Learn Disabil 1991;24:141–146.
100 Lyoo I, Noam G, Lee C, Lee H, Kennedy B, Renshaw P: The corpus callosum and lateral ventricles in children with attention-deficit hyperactivity disorder: a brain magnetic resonance imaging study. Biol Psychiatry 1996;40:1060–1063.
101 O'Kusky J, Strauss E, Kosaka B, Wada J, Li D, Druhan M, Petrie J: The corpus callosum is larger with right-hemisphere cerebral speech dominance. Ann Neurol 1988;24:379–383.
102 Witelson SF: Hand and sex differences in the isthmus and genu of the human corpus callosum: a postmortem morphological study. Brain 1989;112:799–835.
103 Plessen KJ, Bansal R, Zhu H, Whiteman R, Amat J, Quackenbush GA, Martin L, Durkin K, Blair C, Royal J, Hugdahl K, Peterson BS: Hippocampus and amygdala morphology in attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 2006;63:795–807.
104 Shaw P, Eckstrand K, Sharp W, Blumenthal J, Lerch JP, Greenstein D, Clasen L, Evans A, Giedd J, Rapoport JL: Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proc Natl Acad Sci USA 2007;104:19649–19654.
105 Toga AW, Thompson PM, Sowell ER: Mapping brain maturation. Trends Neurosci 2006;29:148–159.
106 Max JE, Manes FF, Robertson BA, Mathews K, Fox PT, Lancaster J: Prefrontal and executive attention network lesions and the development of attention-deficit/hyperactivity symptomatology. J Am Acad Child Adolesc Psychiatry 2005;44:443–450.
107 Heilman KM, Valenstein E: Clinical Neuropsychology. New York, Oxford University Press, 1985.
108 Mesulam MM: From sensation to cognition. Brain 1998;121:1013–1052.
109 Catani M, Howard RJ, Pajevic S, Jones DK: Virtual in vivo interactive dissection of white matter fasciculi in the human brain. Neuroimage 2002;17:77–94.
110 Makris N, Kennedy DN, McInerney S, Sorensen AG, Wang R, Caviness VS Jr, Pandya DN: Segmentation of subcomponents within the superior longitudinal fascicle in humans: a quantitative, in vivo, DT-MRI study. Cereb Cortex 2005;15:854–869.
111 Makris N, Pandya DN, Normandin JJ: Quantitative DT-MRI investigations of the human cingulum bundle. CNS Spectr 2002;7:522–528.
112 Makris N, Worth AJ, Sorensen AG, Papadimitriou GM, Wu O, Reese TG, Wedeen VJ, Davis TL, Stakes JW, Caviness VS, Kaplan E, Rosen BR, Pandya DN, Kennedy DN: Morphometry of in vivo human white matter association pathways with diffusion-weighted magnetic resonance imaging. Ann Neurol 1997;42:951–962.
113 Mori S, Crain BJ, Chacko VP, van Zijl PC: Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. Ann Neurol 1999;45:265–269.
114 Mufson EJ, Pandya DN: Some observations on the course and composition of the cingulum bundle in the rhesus monkey. J Comp Neurol 1984;225:31–43.
115 Petrides M, Pandya DN: Projections to the frontal cortex from the posterior parietal region in the rhesus monkey. J Comp Neurol 1984;228:105–116.
116 Schmahmann JD, Pandya DN: Fiber Pathways of the Brain. New York, Oxford University Press, 2006.
117 Seltzer B, Pandya DN: Further observations on parieto-temporal connections in the rhesus monkey. Exp Brain Res 1984;55:301–312.
118 Banich MT: Cognitive Neuroscience and Neuropsychology. Boston, Houghton Mifflin Company, 2004.
119 Lezak M: Neuropsychological Assessment. New York, Oxford University Press, 1983.
120 Damasio AR, Benton AL: Impairment of hand movements under visual guidance. Neurology 1979;29:170–174.
121 Hecaen H, Albert ML: Human Neuropsychology. New York, Oxford University Press, 1978.
122 Luria A: Human Brain and Psychological Processes. New York, Harper and Row, 1966.
123 Luria A: The Working Brain: An Introduction to Neuropsychology. New York, Basic Books, 1973.
124 Seron X: Neuropsychological analysis of prefrontal lesions in man (in French). Annee Psychol 1978;1:183–202.
125 Damasio AR: Frontal lobes; in Heilman KM, Valenstein E (eds): Clinical Neuropsychology. New York, Oxford University Press, 1985.
126 Biederman J, Monuteaux MC, Doyle AE, Seidman LJ, Wilens TE, Ferrero F, Morgan CL, Faraone SV: Impact of executive function deficits and attention-deficit/hyperactivity disorder (ADHD) on academic outcomes in children. J Consult Clin Psychol 2004;72:757–766.
127 Makris N, Meyer JW, Bates JF, Yeterian EH, Kennedy DN, Caviness VS: MRI-based topographic parcellation of human cerebral white matter and nuclei. II. Rationale and applications with systematics of cerebral connectivity. Neuroimage 1999;9:18–45.
128 Cavada C, Goldman-Rakic PS: Topographic segregation of corticostriatal projections from posterior parietal subdivisions in the macaque monkey. Neuroscience 1991;42:683–696.
129 Flaherty AW, Graybiel AM: Input-output organization of the sensorimotor striatum in the squirrel monkey. J Neurosci 1994;14:599–610.
130 Goldman PS, Nauta WJ: An intricately patterned prefronto-caudate projection in the rhesus monkey. J Comp Neurol 1977;72:369–386.
131 Inase M, Sakai ST, Tanji J: Overlapping corticostriatal projections from the supplementary motor area and the primary motor cortex in the macaque monkey: an anterograde double labeling study. J Comp Neurol 1996;373:283–296.
132 Kemp JM, Powell TP: The cortico-striate projection in the monkey. Brain 1970;93:525–546.
133 Kunzle H: Bilateral projections from precentral motor cortex to the putamen and other parts of the basal ganglia: an autoradiographic study in *Macaca fascicularis*. Brain Res 1975;88:195–209.
134 Kunzle H: Projections from the primary somatosensory cortex to basal ganglia and thalamus in the monkey. Exp Brain Res 1977;30:481–492.
135 Parthasarathy HB, Schall JD, Graybiel AM: Distributed but convergent ordering of corticostriatal projections: analysis of the frontal eye field and the supplementary eye field in the macaque monkey. J Neurosci 1992;12:4468–4488.
136 Saint-Cyr JA, Ungerleider LG, Desimone R: Organization of visual cortical inputs to the striatum and subsequent outputs to the pallido-nigral complex in the monkey. J Comp Neurol 1990;298:129–156.

137 Selemon LD, Goldman-Rakic PS: Topographic intermingling of striatonigral and striatopallidal neurons in the rhesus monkey. J Comp Neurol 1990;297:359–376.
138 Webster MJ, Bachevalier J, Ungerleider LG: Subcortical connections of inferior temporal areas TE and TEO in macaque monkeys. J Comp Neurol 1993;335:73–91.
139 Yeterian EH, Pandya DN: Corticothalamic connections of the posterior parietal cortex in the rhesus monkey. J Comp Neurol 1985; 237:408–426.
140 Yeterian EH, Pandya DN: Corticothalamic connections of paralimbic regions in the rhesus monkey. J Comp Neurol 1988;269: 130–146.
141 Yeterian EH, Pandya DN: Prefrontostriatal connections in relation to cortical architectonic organization in rhesus monkeys. J Comp Neurol 1991;312:43–67.
142 Yeterian EH, Pandya DN: Striatal connections of the parietal association cortices in rhesus monkeys. J Comp Neurol 1993;332: 175–197.
143 Yeterian EH, Pandya DN: Laminar origin of striatal and thalamic projections of the prefrontal cortex in rhesus monkeys. Exp Brain Res 1994;99:383–398.
144 Yeterian EH, Pandya DN: Corticostriatal connections of extrastriate visual areas in rhesus monkeys. J Comp Neurol 1995;352: 436–457.
145 Desmond JE, Gabrieli JD, Glover GH: Dissociation of frontal and cerebellar activity in a cognitive task: evidence for a distinction between selection and search. Neuroimage 1998;7:368–376.
146 Haines DE, Dietrichs E, Mihailoff GA, McDonald EF: The cerebellar-hypothalamic axis: basic circuits and clinical observations. Int Rev Neurobiol 1997;41:83–107.
147 Leiner HC, Leiner AL, Dow RS: Does the cerebellum contribute to mental skills? Behav Neurosci 1986;100:443–454.
148 Parsons LM, Fox PT: Sensory and cognitive functions. Int Rev Neurobiol 1997;41:255–271.
149 Schmahmann JD: An emerging concept: the cerebellar contribution to higher function. Arch Neurol 1991;48:1178–1187.
150 Schmahmann JD, Pandya DN: The cerebrocerebellar system. Int Rev Neurobiol 1997;41:31–60.
151 Schmahmann JD, Sherman JC: Cerebellar cognitive affective syndrome. Int Rev Neurobiol 1997;41:433–440.
152 Schmahmann JD, Sherman JC: The cerebellar cognitive affective syndrome. Brain 1998;121:561–579.
153 Middleton FA, Strick PL: Anatomical evidence for cerebellar and basal ganglia involvement in higher cognitive function. Science 1994;266:458–461.
154 Thach WT, Jones EG: The cerebellar dentatothalamic connection: terminal field, lamellae, rods and somatotopy. Brain Res 1979;169:168–172.
155 Pitcher TM, Piek JP, Hay DA: Fine and gross motor ability in males with ADHD. Dev Med Child Neurol 2003;45:525–535.
156 Pitcher TM, Piek JP, Barrett NC: Timing and force control in boys with attention deficit hyperactivity disorder: subtype differences and the effect of comorbid developmental coordination disorder. Hum Mov Sci 2002;21:919–945.
157 Alheid GF, Heimer L: New perspectives in basal forebrain organization of special relevance for neuropsychiatric disorders: the striatopallidal, amygdaloid, and corticopetal components of substantia innominata. Neuroscience 1988;27:1–39.
158 Bowirrat A, Oscar-Berman M: Relationship between dopaminergic neurotransmission, alcoholism, and reward deficiency syndrome. Am J Med Genet B Neuropsychiatr Genet 2005;132:29–37.
159 Breiter HC, Gasic GP, Makris N: Imaging the neural systems for motivated behavior and their dysfunction in neuropsychiatric illness; in Deiboeck TS, Kersh JY (eds): Complex Systems Science in Biomedicine. Heidelberg, Springer, 2006.
160 Everitt BJ, Parkinson JA, Olmstead MC, Arroyo M, Robledo P, Robbins TW: Associative processes in addiction and reward: the role of amygdala-ventral striatal subsystems. Ann NY Acad Sci 1999;877:412–438.
161 Groenewegen HJ, Berendse HW, Wolters JG, Lohman AH: The anatomical relationship of the prefrontal cortex with the striatopallidal system, the thalamus and the amygdala: evidence for a parallel organization. Prog Brain Res 1990;85:95–116, discussion 116–118.
162 LeDoux JE, Farb CR, Romanski LM: Overlapping projections to the amygdala and striatum from auditory processing areas of the thalamus and cortex. Neurosci Lett 1991;134:139–144.
163 LeDoux JE, Iwata J, Cicchetti P, Reis DJ: Different projections of the central amygdaloid nucleus mediate autonomic and behavioral correlates of conditioned fear. J Neurosci 1988;8:2517–2529.
164 Price JL: Prefrontal cortical networks related to visceral function and mood. Ann NY Acad Sci 1999;877:383–396.
165 Schoenbaum G, Chiba AA, Gallagher M: Orbitofrontal cortex and basolateral amygdala encode expected outcomes during learning. Nat Neurosci 1998;1:155–159.
166 Sonuga-Barke EJ: Causal models of attention-deficit/hyperactivity disorder: from common simple deficits to multiple developmental pathways. Biol Psychiatry 2005; 57:1231–1238.
167 McAlonan GM, Cheung V, Cheung C, Chua SE, Murphy DG, Suckling J, Tai KS, Yip LK, Leung P, Ho TP: Mapping brain structure in attention deficit-hyperactivity disorder: a voxel-based MRI study of regional grey and white matter volume. Psychiatry Res 2007;154:171–180.
168 Blum K, Sheridan PJ, Wood RC, Braverman ER, Chen TJ, Cull JG, Comings DE: The D_2 dopamine receptor gene as a determinant of reward deficiency syndrome. J R Soc Med 1996;89:396–400.
169 Oscar-Berman M, Bowirrat A: Genetic influences in emotional dysfunction and alcoholism-related brain damage. Neuropsychiatr Dis Treat 2005;1:211–229.
170 Gottesman II, Gould TD: The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry 2003; 160:636–645.
171 Meyer-Lindenberg A, Weinberger DR: Intermediate phenotypes and genetic mechanisms of psychiatric disorders. Nat Rev Neurosci 2006;7:818–827.
172 Hyman SE, Nestler EJ: The Molecular Foundations of Psychiatry. Washinton, American Psychiatric Press, 1993.
173 Durston S, Fossella JA, Casey BJ, Hulshoff Pol HE, Galvan A, Schnack HG, Steenhuis MP, Minderaa RB, Buitelaar JK, Kahn RS, van Engeland H: Differential effects of DRD4 and DAT1 genotype on fronto-striatal gray matter volumes in a sample of subjects with attention deficit hyperactivity disorder, their unaffected siblings, and controls. Mol Psychiatry 2005;10:678–685.
174 Castellanos FX: Toward a pathophysiology of attention-deficit/hyperactivity disorder. Clin Pediatr (Phila) 1997;36:381–393.
175 Faraone SV, Biederman J: Neurobiology of attention-deficit hyperactivity disorder. Biol Psychiatry 1998;44:951–958.