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

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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.

Keywords

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

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 systems 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 Fig. 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 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 (DTMRI) 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 sublentiform 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 disorder [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 other 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-striatal 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 T1-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.

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

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.

Fig. 3.

Conceptual model of the neuroanatomical substrates of ADHD. AMF = Amygdalo-fugal pathway; MB = Muratoff 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.