Published in final edited form as:

Curr Psychiatry Rep. 2012 October ; 14(5): . doi:10.1007/s11920-012-0310-y.

Neuroimaging of Attention-Deficit/Hyperactivity Disorder: Current Neuroscience-Informed Perspectives for Clinicians

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Abstract

The neuroimaging literature of Attention-Deficit/Hyperactivity Disorder (ADHD) is growing rapidly. Here, we provide a critical overview of neuroimaging studies published recently, highlighting perspectives that may be of relevance for clinicians. After a comprehensive search of PubMed, Ovid, Web of Science, and EMBASE, we located 41 pertinent papers published between January 2011 and April 2012, comprising both structural and functional neuroimaging studies. This literature is increasingly contributing to the notion that the pathophysiology of ADHD reflects abnormal interplay among large-scale brain circuits. Moreover, recent studies have begun to illuminate the mechanisms of action of pharmacological treatments. Finally, imaging studies with a developmental perspective are revealing the brain correlates of ADHD over the lifespan, complementing clinical observations on the phenotypic continuity and discontinuity of the disorder. However, despite the increasing potential to eventually inform clinical practice, current imaging studies do not have validated applications in day-to-day clinical practice. Although novel analytical tools will likely accelerate the pace of translational applications, at the present time we caution regarding the inappropriate commercial misuse of imaging techniques in ADHD.

Keywords

ADHD; neuroscience; neuroimaging; MRI

Introduction

The neuroimaging literature on Attention-Deficit/Hyperactivity Disorder (ADHD) is growing rapidly. For example, a Pubmed search of “ADHD AND imaging” in 2001 retrieved 26 references, 81 in 2005, and 141 in 2010. This growth has been accompanied by: 1) a shift in the neurobiological conceptualization of ADHD from a primarily fronto-striatal disorder to a condition characterized by abnormal interplay among several structurally and functionally defined brain networks; 2) the introduction of new neuroimaging techniques; and 3) the use of increasingly sophisticated analytical approaches. Clinicians may find it

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challenging to stay abreast of this growing and complex literature. Here, we provide an overview of salient trends in the neuroimaging research on ADHD published recently (from January 2011 to April 2012), highlighting the emergence of themes and perspectives that are or may become relevant for clinical practice. We present key findings from two main types of neuroimaging studies: 1) structural, including voxel based morphometry (VBM), cortical thickness, and diffusion tensor imaging (DTI) measures, and 2) functional, whether task-based functional MRI (fMRI), resting state MRI (R-fMRI), near-infrared spectroscopy, positron emission tomography (PET) or single-photon emission computed tomography (SPECT). We also review recent neuroimaging studies aiming at elucidating the mechanism of action and/or effectiveness of ADHD treatments.

Methods

Study search

Although not strictly speaking a systematic review, since we did not conduct a detailed appraisal of the quality of the reviewed studies, we performed a comprehensive search across a broad set of databases using a large number of search terms to minimize the chance of missing relevant studies. We searched PubMed, Ovid (including PsycINFO and Ovid MEDLINE®), Web of Science (SCI-EXPANDED, SSCI, A&HCI), and EMBASE from 01.01.2011 to 04.14.2012. The search terms, adapted for each database, are reported in the Supplementary Material.

Inclusion and exclusion criteria

We included empirical studies using any neuroimaging technique. Only studies where the diagnosis of ADHD was performed according to standard criteria (DSM-IV or ICD-10) were retained. Studies that included only individuals with ADHD plus specific comorbidities (e.g., ADHD+Bipolar Disorder) were excluded as were abstracts of conference presentations. Given the hard-won recognition by the field of the importance of correction for multiple comparisons in neuroimaging analyses, we excluded studies that did not correct for multiple comparisons or in which the use of correction methods was unclear. Finally, we excluded fMRI studies with sample sizes <15 per group as underpowered studies are most likely to report type I errors [1].

Results

Figure 1 shows the search results according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart [2]. A total of 41 [3-43] studies were retained, which are discussed below.

Discussion

Structural imaging

Most of the early structural MRI studies in ADHD contrasted individuals with ADHD and comparisons to identify ADHD-related differences. This large body of research was summarized recently in two meta-analyses [16;26] with complementary methods, largely overlapping included studies, and converging results. Pooling 14 VBM datasets including 378 individuals with ADHD and 344 comparisons, Nakao et al. [26] found a significant reduction of gray matter volume in the right basal ganglia (putamen, globus pallidus, and caudate), in line with fronto-striatal models of ADHD pathophysiology. Interestingly, estimates of right putamen gray matter volume increased with age, suggesting that ADHD patients partially “outgrow” basal ganglia deficits. Reduced right globus pallidus and putamen volumes were also found by Frodl et al. [16] in a meta-analysis of 11 VBM studies,

encompassing 320 individuals with ADHD and 288 comparisons (all of which were included in Nakao et al. [26]). The two meta-analyses also addressed an issue of concern to patients and clinicians, i.e., the possible effect of ADHD drugs on brain structure. Both Nakao et al. [26] and Frodl et al. [16] provide suggestive VBM evidence that stimulants are associated with reduction or even normalization of structural abnormalities in ADHD. Frodl et al. [16] also examined eight studies in which caudate volumes were hand-traced and found significant evidence for decreased volumetric reductions in bilateral caudate in studies with a higher proportion of stimulant treated subjects [16].

Concern regarding disentangling correlates of the diagnosis from possible consequences of medication treatment has increasingly motivated participant selection. In a study of 31 adults with ADHD and 31 comparisons in which only one patient had ever been treated with stimulants and all participants were medication-free for at least 6 months, Ahrendts et al. [3] found significant gray matter volume reduction only in bilateral visual cortex. The authors interpreted these unexpected occipital findings as expression of impairments in early-stage 'subexecutive' attentional mechanisms. Similarly, Almeida Montes et al. [4], focusing on cerebellar morphometry in females, included only stimulant-naïve children, adolescents and adults, concluding that cerebellar volumetric reductions are not ascribable to stimulant treatment. Other recent studies have continued to confirm the notion that ADHD is characterized by structural abnormalities in fronto-striatal [6;24;35] and cerebellar regions [4;7].

Another recent trend in structural studies has been a focus on cortical thickness, which defines gray matter regions with high spatial resolution [30]. Contrary to other reports in ADHD, Duerden et al. [15] found significantly increased cortical thickness in primary sensorimotor cortex in 13 adults with ADHD vs. 20 comparisons. These effects were largely accounted for by loss of age-related decreases in cortical thickness in ADHD, which supported the speculation that they reflect maturational abnormalities. Another cross-sectional study in medication-naïve children, adolescents, and adults reported significantly reduced cortical thickness in ADHD vs. comparisons predominantly in frontoparietal regions, as well as increased cortical thickness primarily in occipital regions, in all age groups [5].

A limitation of studies of adults with ADHD has been reliance on retrospective reports of childhood symptoms for the diagnosis of ADHD, which may be problematic [44]. This was bypassed in a study assessing cortical thickness and VBM at 33-year follow-up in 59 adults with ADHD established in childhood (probands) and 80 comparisons free of ADHD in childhood [30]. Proal et al. [30] found significantly thinner cortex in ADHD probands than in comparisons in the dorsal attentional network and limbic areas [30]. Subcortically, gray matter volume was significantly decreased in ADHD probands vs. comparisons in the right caudate, right thalamus, and bilateral cerebellar hemispheres. Results were largely independent of whether ADHD was ongoing (n=17) or had remitted (n=26), suggesting that many structural brain differences endure in individuals with a childhood history of ADHD regardless of current ADHD status in adulthood [30].

Befitting its status as a neurodevelopmental disorder, ADHD investigators have increasingly focused on developmental trajectories. In this regard, the NIMH group has long been at the forefront. Most recently, they reported a significantly higher rate of growth in the most anterior region of the corpus callosum in 236 right-handed participants with ADHD than in 230 comparisons scanned at mean age 10, 12, 15, and 17 [18]. This study highlights the dynamic nature of ADHD-related structural abnormalities, which may reflect the changes in the clinical presentation of ADHD during development, although this hypothesis has not been directly tested. From a developmental perspective, we note the publication of the first

study [23] examining regional cortical and subcortical brain volumes in preschool children with ADHD. Mahone et al. [23] found significantly reduced caudate volumes bilaterally in 11 medication-naïve preschoolers with ADHD vs. 13 comparisons (ages 4-5 years). Left caudate volume significantly predicted hyperactive/impulsive, but not inattentive symptom severity. As the sample size in this pioneering study was marginal, the lack of significant group differences outside the caudate should not be interpreted as definitive.

As ADHD is increasingly conceptualized as a disorder of altered connections within and among neuronal networks, DTI studies have been conducted to assess possible structural anomalies in principal white matter tracts. A recent contribution [25] reported the first DTI study conducted exclusively in prepubertal children who were largely medication free. Besides replicating previously reported structural anomalies in white matter tracts implicated in higher-order cognitive functions, Nagel et al. [25] also found a novel alteration in the frontolimbic tract, which is implicated in emotional functions, in line with increasing clinical attention to emotional dysregulation in ADHD [45]. The authors noted that the frontolimbic tract is among the last WM tracts to mature and that developmental effects may be detectable in ADHD that are no longer observable in older children or adults. The authors also suggested that WM alterations may be an early marker of ADHD rather than reflecting compensatory restructuring. Another recent DTI study by Dramsdahl et al. [14] has extended our knowledge on WM abnormalities in adults, showing that, despite a lack of macrostructural abnormalities in the corpus callosum, DTI revealed ADHD-related microstructural abnormalities in the isthmus-splenium. Dramsdahl et al. [14] suggested that, while adults may have compensated for macrostructural callosal abnormalities often found in children, they still presented microstructural alterations that may underpin impairments in auditory and speech perception functions subserved by fibers crossing the isthmus-splenium. They noted that possible auditory and speech perception deficits are rarely considered when adults with ADHD are evaluated clinically.

Studies of DTI in children with ADHD have confirmed diffuse abnormalities in a large set of white matter clusters, rather than in restricted regions [27;31]. The ADHD DTI literature has advanced sufficiently to support an initial meta-analysis. Pooling data from nine studies, Van Ewijk and colleagues [39] reported consistent abnormalities in a large cluster in the right anterior corona radiata and in another cluster in the left cerebellar WM as well as in additional clusters in the internal capsule. All the tracts identified meta-analytically connect brain areas implicated in the pathophysiology of ADHD.

Diffusion based imaging methods are also being extended to extract even more information regarding brain microstructure. One such novel approach is referred to as diffusional kurtosis imaging (DKI), which uniquely allows the quantification of the microstructural integrity of both gray and white matter, even in the presence of crossing fibers, a well known limitation of classic DTI. A preliminary application of DKI in 12 adolescents with ADHD and 13 typically developing children (TDC) found a lack of age-related increase of WM complexity in the ADHD group, in contrast to the TDC participants [19].

A convergence of approaches has begun to illuminate the genetic and environmental underpinnings of brain alterations. However, combining imaging and genetics methods requires substantial sample sizes. For example, de Zeeuw et al. [13] were able to draw on a data set of over 300 to investigate the effects of prenatal exposure to cigarettes and alcohol in the context of ADHD. At mean age ~ 10 years, ADHD children exposed antenatally to cigarettes had the smallest cerebellum volumes of the analyzed subgroups. Those with ADHD who had not been exposed to nicotine or alcohol prenatally had intermediate cerebellar volumes, and unexposed controls had the largest cerebellar volumes. The stair step pattern of results suggests that both genetic and environmental effects likely impact

brain structure, and children with ADHD who are prenatally exposed to cigarettes or alcohol may suffer from a ‘double hit,’ with clear clinical and public health implications.

In summary, recent structural studies of ADHD have extended classical ADHD models of ADHD pathophysiology focused on cerebellar-frontal-striatal models by including a broader range of brain regions, including subregions within temporal and occipital cortex. Recent studies have extended the ages at which ADHD is examined to as young as preschoolers and into middle-adulthood, and investigators are continuing to begin to explore the genetic/environmental underpinnings of the brain correlates of ADHD. As analytical methods continue to improve (e.g., [21]) we can expect further advances in our knowledge of the structural brain anomalies underpinning ADHD.

Functional studies

Similarly to structural studies, functional studies of ADHD have primarily reported differences among groups, which are useful in advancing understanding of the underlying pathophysiology but which are not relevant to clinical practice. However, shifts in the conceptualization of ADHD, evolution of methods and analytical tools, and collaborative efforts among scientists throughout the world are changing perspectives and bringing closer the time when functional imaging in ADHD will be relevant to day-to-day clinical practice. Specifically, the recent functional imaging literature has begun to address the hypothesis that at least some of the symptoms manifested by individuals with ADHD can be ascribed to abnormal regulation of large-scale brain networks, with much of the focus being placed on the brain’s default network [46].

Functional imagers have recently taken note of the startling degree of synchrony exhibited by brain regions even in the absence of specific cognitive or motor tasks. So-called resting state functional MRI (R-fMRI), consists of obtaining blood-oxygen level dependent (BOLD) signals for several minutes, and then examining the intrinsic patterns of activity [46]. Such data are amenable to a wide range of analytic methods [47] which reveal large-scale brain networks that replicate across labs and that are substantially stable in test-retest analyses [48]. The most frequently examined intrinsic brain connectivity network (also referred to as a “resting state network”) was named the brain’s default network (DN) by Raichle and colleagues [46]. The DN is defined by low-frequency synchronous spontaneous activity in medial prefrontal, medial parietal, lateral temporal and medial temporal regions [49]. The amplitude of DN fluctuations is systematically attenuated during externally-oriented attention, and amplified during self-oriented processing or during task-unrelated thoughts [50]. Simultaneous observation of DN and fronto-parietal regions shows a reciprocal pattern of activity – described as anticorrelations [51], which led Sonuga-Barke and Castellanos to propose the DN hypothesis of ADHD [52]. They suggested the DN might be inadequately regulated by other task-active systems, and might consequently intrude on or disrupt ongoing cognitive performance, contributing to the spontaneous fluctuations in attention that appear to characterize ADHD. This hypothesis has begun to be examined directly.

A meta-analysis of task-based fMRI studies published up through June 2011 [10] showed that most of the hyperactivated regions in contrasts of ADHD vs. comparisons were located in the DN, as predicted by the DN hypothesis of ADHD. Other studies that were not included in the meta-analysis (because they were published after June 2011) are also germane. Sun et al. found decreased anticorrelation between the dorsal anterior cingulate cortex (dACC) (a component of the task positive network) and the DN, replicating an initial observation in adults with ADHD [53]. Liddle and colleagues [22] showed that children with ADHD did not deactivate the DN during a task in relation to comparisons when off methylphenidate and under low motivational incentives, but the groups did not differ significantly when the ADHD children received high motivational incentives or were treated

with methylphenidate. They concluded either motivational incentives or methylphenidate may normalize abnormal deactivation of the DN in ADHD.

Examination of the DN during rest was used to compare children with ADHD (n=37) and typically developing children (n=37) in relation to externalizing and internalizing scores on the Child Behavior Checklist [8]. On one hand, significant associations were found between increasing internalizing scores and stronger positive intra-DN intrinsic functional connectivity (iFC) as well as between increased externalizing scores and reduced negative iFC between DN and task-positive regions such as dACC, regardless of diagnostic group. On the other hand, some brain-behavior relationships differed between groups. Despite the exhortation that investigations of psychopathology should adopt a primarily dimensional approach [54], these data suggest that dimensional and categorical approaches will need to be combined in developing mechanistic models of psychopathology. Still, the power of dimensional analysis was suggested by an analysis conducted by Shaw et al. who reported dimensional relationships between the rate of cortical thinning in TDC in relation to the extent of ADHD symptoms, from none, minimal, to moderate, with the rate approximating that of children with ADHD [36].

Categorical contrasts among ADHD, autism spectrum disorders (ASD) and healthy comparisons (n=20 per group) found lack of suppression in the posterior node of the DN, in the precuneus, in both patient groups [9]. Within each group, precuneus activity was significantly negatively correlated with prefrontal activation, lending support to the DN hypothesis for both ADHD and ASD. Additionally, they found deficits that were disorder-specific. Specifically, left dorsolateral prefrontal cortex underactivation, which was related to task performance, was only found in ADHD. This study presages the upcoming revision of diagnostic criteria for ADHD in DSM-5 which are expected to allow the co-application of diagnoses of ADHD and ASD.

Another example of looking for common and unique results was conducted in 20 adults with ADHD and 24 comparisons who underwent fMRI with three tasks tapping interference inhibition, action withholding and action cancellation. The latter two tasks produced basal ganglia hypoactivations, whereas interference inhibition resulted in midcingulate and temporal lobe hypoactivations in ADHD. This study thus added to the growing awareness that multiple neural networks are implicated in ADHD can be identified via a range of task probes [34].

As noted in our review of structural studies, investigators have been increasingly focusing on emotional reactivity in ADHD. A functional comparison of 15 adolescents with ADHD and 15 healthy comparisons during subliminal presentation of fearful faces revealed atypical processing of fear in ADHD [28]. Adolescents with ADHD also exhibited significantly greater effective connectivity between amygdala and lateral prefrontal cortex.

An impressive fMRI study examined both BOLD signal and skin conductance in 28 adults with ADHD and 28 comparisons using a card-guessing task in which incentive and outcomes were manipulated. This well-powered and rigorously designed study found that medial orbitofrontal cortex activation coded for reward value in controls but not in the patients with ADHD [42]. The imaging results were corroborated by findings on tasks of delay discounting and impulsive decision making. In patients with ADHD, neural signals in medial orbitofrontal cortex were dysregulated – overvaluing low-incentive rewards and undervaluing high-incentive monetary rewards. The authors conclude that these atypical patterns of neural behavior in a key circuit related to self-regulation and complex decision making are likely to be relevant to the emotional and motivational challenges encountered by adults with ADHD.

While the bulk of functional imaging studies use MRI, PET and SPECT have an unarguable advantage for probing specific neural systems such as dopaminergic function in vivo [12]. Volkow et al. [40] re-examined PET measures of D2/D3 receptor and dopamine transporter availability in the midbrain and nucleus accumbens and related them to a surrogate measure of motivation. They found disruption of the brain dopamine reward pathway in 45 adults with ADHD relative to 41 controls, which was related to symptoms of inattention in participants with ADHD, thus linking core symptoms of inattention to the broader construct of motivational processes in ADHD.

In summary, besides the classical task-based cross-sectional studies and PET/SPECT studies, the increasing number of resting state functional studies has the potential to provide a more comprehensive picture of complexity of networks involved in ADHD. In the near future, these can be expected to provide neuroimaging tools to complement the diagnostic and prognostic process at the single subject level. As findings using expensive or invasive methods are increasingly validated, we anticipate that they will be extended to other approaches that may be more amenable to clinical settings. Two well-designed, studies using functional near-infrared spectroscopy [32;33] provides an illustrative early example of this process. Another example of a preliminary report with possible clinical implications was provided by Cortese et al. who contrasted 18 children with ADHD to 18 comparisons, half of whom were healthy and the other half with non-ADHD psychiatric conditions on an MRI index of brain iron levels [11]. They found significantly decreased T2* in bilateral thalamus which was interpreted as evidence of deficient brain iron, which is essential for myelination and monoaminergic metabolism. Confirmation of this pilot result with newer methods [55] would raise the issue of whether such brain iron abnormalities can be modified through dietary supplementation.

Neuroimaging studies of ADHD treatments

Studies of the mechanism of action of ADHD drugs or investigations assessing the brain correlates of ADHD treatments are of particular interest to clinicians. A preliminary meta-analysis of dopamine transporter availability, measured with PET or single photon emission computed tomography [17] tentatively concluded that reports of increased dopamine transporter availability in ADHD likely reflect a history of treatment with stimulants, rather than the neurobiology underlying the disorder. Relatedly, Volkow et al. showed that a challenge dose of 0.5 mg/kg intravenous methylphenidate significantly increased dopamine in striatum and these dopamine increases were associated with reductions in ratings of inattention [41].

Normalization of medial prefrontal cortex activity by stimulant treatment was demonstrated using cognitive and emotional versions of the Stroop task in 15 adolescents with ADHD scanned both on and off medication [29]. Wong and Stevens conducted a randomized double-blind placebo-controlled in conjunction with fMRI during the Sternberg working memory task in 18 adolescents with ADHD [43]. They observed that methylphenidate leads to strengthened connectivity of some frontoparietal regions, which may underlie the improvement in reaction time observed during a working memory task.

Besides this body of research focusing on pharmacological treatment, we note a study showing volumetric gray matter increases in bilateral middle frontal cortex and right inferior-posterior cerebellum after cognitive training in 18 children with ADHD vs. 18 comparisons [20]. Of note, gray matter volume increase in the inferior-posterior cerebellum was associated with improved attentional performance. If replicated independently in larger samples, these results would engender substantial enthusiasm.

Conclusions

The recent neuroimaging literature continues to contribute to emerging models of the pathophysiological mechanisms underpinning ADHD. This maturing field provides substantial evidence implicating frontal-striatal and cerebellar regions in ADHD while also supporting the inclusion of interactions among extra-frontal regions detected during specific tasks or even during “rest.”

Emerging results relevant to clinical practice include findings that many brain structural differences continue to be evident in ADHD in middle adulthood regardless of whether the disorder persists or has remitted [30]. Such enduring alterations are likely ascribable to genetic factors, but they may also reflect prenatal exposures such as nicotine or alcohol [13]. While randomized controlled long-term trials of stimulant treatment will never be conducted in humans for obvious ethical reasons, indirect accumulating evidence suggests that stimulants produce normalization in brain structure [16;26] and function [22] and that deviations from typical development are not the result of stimulant treatment [4].

One of the dividends from brain imaging studies is the increasing awareness that brain correlates of emotional reactivity [28] and emotional processing [25] are abnormal in groups of individuals with ADHD. Also novel and based in imaging results is the suggestion that auditory and speech perception deficits be considered in clinical and research evaluations of adults with ADHD [14]. Similarly, insistent findings of visual occipital cortex abnormalities in ADHD [3;30] imply that visual perception may be fruitfully reexamined in ADHD [48].

Despite the increasing pace of progress in neuroimaging methods and approaches, claims of clinical utility of neuroimaging-based tools are premature [56] and currently indefensible for the diagnosis of ADHD or for formulation of treatment plans. However, with continued momentum and wide-spread adoption of an ethos of open science [57], we expect that imaging tools will soon be able to support the clinical process, particularly for the disambiguation of the most challenging cases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of retained studies.

* Nineteen studies [1-19] studies were excluded because of sample size <15 (in at least one study subgroup). One study [20] was discarded since results were based on analyses uncorrected for multiple comparisons. Two studies [21;22] assessed individuals with self-reported ADHD symptoms, without a formal interview, and were therefore excluded. One was not an original empirical study [23]. Finally, we did not include two studies that examined, respectively, individuals with ADHD plus Bipolar Disorder [24] and ADHD plus developmental coordination disorder [25]. References of excluded studies are reported in the Supplemental Material (SM 2).