Recent Advances in Structural and Functional Brain Imaging Studies of Attention-deficit/Hyperactivity Disorder

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The field of neuroimaging of attention-deficit/hyperactivity disorder (ADHD) is now 30 years old. This brief selective review highlights the increasing sophistication of recent structural and functional neuroimaging studies of ADHD. In volumetric studies, investigators are examining extra-frontal, as well as frontal-striatal circuits and beginning to differentiate the potential effects of medication exposure. Functional MRI studies are focusing on familial/genetic influences and enrolling medication naïve, as well as medicated children with ADHD. A promising trend is the application of resting state approaches to mapping functional connectivity, which provides unexpectedly detailed information about interregional relationships while bypassing potentially confounding issues related to task performance. These developments allow us to conclude that neuroimaging studies of ADHD will increasingly inform our understanding of the neuronal substrates of ADHD.

Introduction

As Figure 1 depicts, neuroimaging approaches have been applied to attention-deficit/hyperactivity disorder (ADHD) or to the precursor, "minimal brain dysfunction," for 30 years. The first decade began with computed axial tomography studies, which provided little detail regarding brain parenchyma. Positron emission-based methods were prominent during the second decade, which also saw the beginning of MRI in 1990, coincident with the initiation of the "Decade of the Brain." Methods that exploit the ever-increasing power of MRI now predominate, and the pace of progress is continuing to accelerate. This brief and selective review highlights the trends within the fields of structural and functional neuroimaging that seem to have the greatest momentum.

Structural MRI

Second-generation (ie, quantitative, anatomic neuroimaging) studies, recently reviewed elsewhere both qualitatively [1] and quantitatively [2], demonstrated that ADHD is associated with 1) slightly but significantly smaller total brain volume, 2) particularly prominent effects in the cerebellum, and 3) age-dependent effects in the caudate nucleus, and that smaller cerebral and cerebellar volumes could not be ascribed to prior medication exposure. Recent work has focused on examining previously neglected regions of interest, such as the hippocampus and amygdala [3•]. In an excellent example of this, Plessen et al. [3•] compared a substantial sample of 51 individuals with combined-type ADHD and 63 healthy comparison controls (HCs) aged 6 to 18 years. By subdividing the hippocampus into seven regions, they found that the head of the hippocampus was significantly larger ($P = 0.002$) in ADHD patients, which was weakly related to lower parental ratings of symptom severity ($P < 0.07$). The authors noted that two prior studies had found nonsignificantly larger hippocampal volumes in those with ADHD. Amygdala volumes did not differ between groups, but surface analyses showed reduced size of the bilateral basolateral complexes in ADHD. Interestingly, amygdala volumes were significantly correlated with orbitofrontal cortical grey matter volumes in HCs (right r = 0.66, left r = 0.48; $P < 0.001$), but not in the ADHD group, which differed significantly in magnitude of correlations. These preliminary findings suggest greater involvement of key limbic system regions in the pathophysiology of ADHD than had been previously surmised.

Another relatively neglected key region in volumetric studies is the putamen (although see [1] for lesion and blood flow studies). A small recent study compared 12 male adolescents with combined-type ADHD and psy-

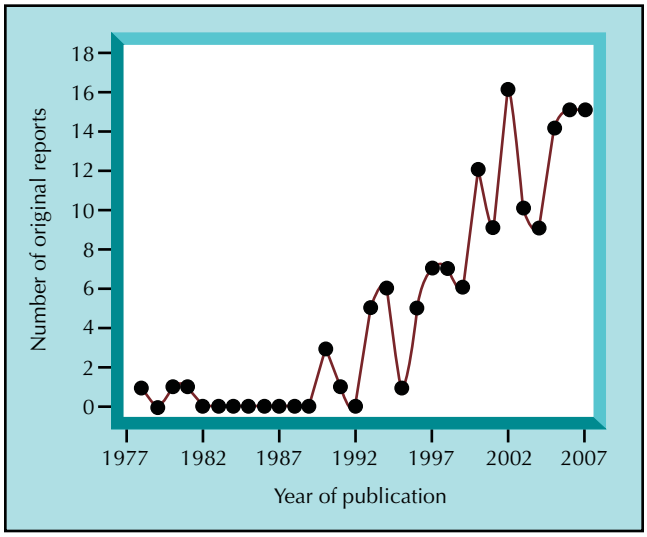

Figure 1. Yearly progression in number of peer-reviewed original reports of anatomic or functional brain imaging studies of attention-deficit/hyperactivity disorder. Studies prior to 1989 used computed axial tomography; total for 2007 is for first 6 months only.

chopathic traits with 12 HCs [4]. No differences in right, left, or total putamen volume were found, but the authors reported a significant ($P = 0.03$) group difference in asymmetry, with the ADHD/psychopathic group exhibiting right-greater-than-left asymmetry, which was the reverse of the comparison group. Unfortunately, ratios such as asymmetry measures are inherently unreliable [5] because reliability decreases inversely with the degree of similarity between the left and right sides. Thus, this finding of putamen asymmetry remains tentative pending independent replication with sufficiently powered samples.

Because of the cost of neuroimaging research, there has been a tendency to publish underpowered studies, which effectively increases the prevalence of type I errors. Fortunately, the field is increasingly requiring larger, more appropriately powered samples. McAlonan et al. [6] performed voxel-based morphometry analyses of grey and white matter in 28 stimulant-treated boys with ADHD and 31 matched control boys (mean age 10 years). They found significantly lower grey matter volumes in predominantly right frontal cortex, globus pallidus, and medial and lateral parietal cortex, including precuneus (Brodmann area 7), superior occipital cortex, and cerebellum, which were largely independent of comorbidity. Exceptions were globus pallidus differences, which were only present in the comorbid ADHD subgroup, and cerebellar differences, which were more prominent in the comorbid subgroup. Lower white matter volumes also were observed bilaterally across frontal, temporal, and parietal lobes in ADHD.

In order to address potential confounds related to medication responses, McAlonan et al. [6] recruited only children with ADHD who were stimulant responders. Pliszka et al. [7] examined anterior cingulate cortex (ACC) and caudate volumes in 21 HCs, 16 stimulant-treated children with ADHD, and 14 treatment-naïve children with ADHD. Whereas both ADHD groups demonstrated lower caudate volumes than controls, only the treatment-naïve group demonstrated reduced ACC volume. The results are consistent with a positive trophic influence of stimulants on ACC, although causation cannot be ascribed in naturalistic designs.

The largest anatomic imaging study in ADHD, which began in 1991 at the National Institute of Mental Health, now includes cross-sectional and longitudinal data from 163 children with ADHD who entered the study at a mean age of 8.9 years and 166 HCs. Shaw et al. [8] examined cortical thickness and found a significant mean global reduction of 0.09 mm in ADHD, which was most prominent in medial and superior prefrontal and precentral regions. Children with worse clinical global outcomes had significantly thinner left medial prefrontal cortex (PFC) at baseline, whereas right parietal cortex thickness normalized in those with better outcomes. These findings converge with a cortical thickness study of 24 adults with ADHD and 18 controls [9]. In that study, Makris et al. [9] found significantly thinner cortex in right inferior parietal lobule, dorsolateral prefrontal cortex (dlPFC), and ACC. Also reported but not discussed was significant thinning in the posterior cingulate cortex, which along with precuneus is emerging as an important new region in resting state functional imaging studies in ADHD, as we will discuss subsequently. In a volumetric examination of these adult data, Seidman et al. [10] found significantly lower grey matter volumes in PFC and ACC. Adults with ADHD also had a larger nucleus accumbens (NAcc) and significantly greater white matter volumes. Although these findings were statistically less robust, the NAcc difference is consistent with reward mechanism alterations in ADHD, whereas the increased white matter volumes may reflect compensatory mechanisms.

An exciting development is the focus on genetic and environmental risk factors in structural studies. A recent report [11•] suggests that such risk factors may be dissociable in their effects on structural abnormalities, which could explain much of the substantial heterogeneity of disorder. White and grey matter volumes were measured in monozygotic twins who were either concordant or discordant on parental ratings on the Child Behavior Checklist Attention Problem Scale, a common measure of inattentive and hyperactive symptoms that reflects risk for ADHD. In the absence of differences in global grey or white matter volumes, the three pairs of concordant high-risk twins showed decreased grey and white matter volumes in orbitofrontal and anterior temporal cortices relative to 17 concordant, low-risk twin pairs, which may reflect genetic risks for ADHD. Reduced white matter volume in posterior corpus callosum and reduced grey matter in adjacent medial parietal cortex also were found, in addition to reduced parietal and occipital white matter. High-risk

children from five discordant twin pairs showed reduced grey matter volumes in right inferior dlPFC and anterior temporal cortex relative to their low-risk twin. The authors suggest that this reflects environment-related risk factors. Excitement about these findings has to be tempered by the exceedingly small samples that are intrinsic to discordant twin designs given the high heritability of ADHD.

Functional Imaging (functional MRI [fMRI])

Dickstein et al. [12] applied a novel voxel-wise quantitative meta-analytic method, Activation Likelihood Estimation [13], to 17 functional neuroimaging studies of ADHD published through 2005. Despite considerable heterogeneity in terms of experimental paradigms, statistical approaches, imaging modality, population characteristics, and generally small samples (mean 12, range 6–21 per group), the meta-analysis detected statistically reduced likelihood of activation for individuals with ADHD in ACC; inferior, medial, and dlPFC; and basal ganglia, thalamus, and portions of parietal cortex ($P < 0.05$, whole brain corrected). The meta-analysis supported previous conclusions regarding hypofrontality in ADHD but also demonstrated the potential role for other loci of dysfunction, such as thalamus, ventral striatum, and parietal cortex.

Recent studies reflect increased recognition that temporal and parietal cortices likely contribute to ADHD-related cognitive deficits. Silk et al. [14] observed reduced activation in inferior and superior parietal cortex and middle frontal cortex in adolescent boys with ADHD. ADHD boys also showed increased activation in superior and middle temporal cortex relative to controls, which may reflect greater use of an object-based rather than spatial approach to the task. Vance et al. [15•] examined the same mental rotation task in 12 children aged 8 to 12 years with combined-type ADHD and 12 HCs using slow, event-related fMRI. The groups did not differ on behavioral differences, though effect sizes were moderate to large ($d > 0.76$). Children with ADHD showed reduced activation in right parietal-occipital areas, inferior parietal lobe (IPL), and caudate, which suggests a right hemisphere parietal spatial attention deficit in ADHD. Based on these two studies in children and adolescents, the authors suggested that the activation deficit is developmental stage independent. On the other hand, some findings were not replicated. The younger sample did not demonstrate group differences in prefrontal activation or the ADHD-related relative increases in temporal and midline parietal areas, suggesting that some group differences for this task are subject to developmental effects, which is not surprising. Despite the consistency of ADHD-related behavioral decrements in spatial working memory, as discussed by Westerberg et al. [16], the neural correlates of such decrements remain in need of considerable further study.

Studies of executive function and attentional control in ADHD have tended to focus on dysfunction in frontostriatal networks, although parietal and temporal involvement is increasingly being recognized. This may reflect increased statistical power from larger samples and the use of medication-naïve samples. For example, Rubia et al. [17•] scanned 17 males aged 9 to 16 years with ADHD and 18 HCs during a combined Go/No-Go and visual oddball task. Participants with ADHD showed significantly increased variability during both standard and oddball trials. Relative to HCs, ADHD participants demonstrated decreased ACC and right dlPFC activation on Go relative to oddball trials. For oddball relative to Go trials, ADHD participants showed reduced activation across a number of areas, including bilateral temporal cortex and left IPL. Furthermore, ADHD and HC showed differential patterns of correlation between activation for oddball trials and behavioral variability. Specifically, whereas HC showed a negative correlation between variability and activation in primarily cortical areas, including inferior PFC/insula and superior temporal cortex, behavioral variability in the ADHD group was negatively correlated with activation in primarily subcortical regions (ie, caudate, putamen, and thalamus, as well as superior temporal cortex). These findings suggest that individuals with ADHD rely on different neural networks for attentional performance, possibly to compensate for insufficient cortical activation.

Differential frontal, temporal, and parietal cortex activation also was reported by Smith et al. [18], who examined a relatively large sample of boys with ADHD who were medication-naïve ($n = 19$, age ~ 13 years) and a sample of comparison boys ($n = 27$, age ~ 14 years) on three tasks; a Go/No-Go with oddball trials, a motor Stroop (also with oddballs), and a visual-spatial switch task. Although performance differences between groups were not significant when age was entered as a covariate in the behavioral analyses, ADHD boys showed significantly less activation than controls in bilateral inferior PFC, superior temporal gyrus, right middle temporal gyrus, and IPL, further supporting a role for dysfunction in these cortical regions in the executive and attentional deficits associated with ADHD.

The role of mesolimbic ventral striatal circuitry in ADHD-related deficits in reward and reinforcement processes has begun to receive attention in the neuroimaging literature. Scheres et al. [19•] examined 11 adolescents with ADHD and 11 HCs during a reward-anticipation paradigm. Participants were presented with a cue that signaled a potentially rewarded response, an unrewarded response, or no response requirement. In reward trials, participants were required to respond to a target while it was on screen in order to receive the monetary reward. The hypothesis that the ADHD and HC groups would differ in magnitude of striatal activation during reward anticipation was supported. Relative to HCs, adolescents with ADHD demonstrated reduced ventral striatal activation during reward anticipation, which was more

pronounced with increasing reward magnitudes (20 cents to $1 to $5). In the sample as a whole, ventral striatal activation was significantly negatively correlated with levels of hyperactivity/impulsivity but not with inattention. These findings provide preliminary support for the hypothesis that ADHD is associated with hyporesponsiveness of the ventral striatum salience circuit during reward anticipation, and that this hyporesponsiveness is specifically related to hyperactive/impulsive behaviors.

One question now being addressed is whether or to what extent more fundamental "lower-level" impairments contribute to previously hypothesized higher-level executive function deficits. Based on evidence implicating frontocerebellar circuits in ADHD and observations that children with ADHD are more variable and less accurate on tasks involving time estimation, Durston et al. [20•] hypothesized that frontocerebellar dysfunction in ADHD may lead to deficits in the ability to predict both the occurrence and timing of events. Two samples of children (10 ADHD and 10 HCs in one sample with mean age ~ 12 years; 12 in each group in the second, mean age 15 years) were scanned in a modified Go/No-Go paradigm in which predictability of stimulus timing and identity (ie, No-Go trials) were manipulated. The majority of trials (76%) were predictable in type (Go trials) and timing (a trial every 4 seconds), whereas 24% of trials were unpredictable. In these cases, either the expected Go stimulus was presented at an unexpected time (2 seconds), or an unexpected (No-Go) stimulus was presented at the expected (4 seconds) or at an unexpected (2 seconds) time. Children and adolescents with ADHD were more variable and less accurate for trials at unexpected times and No-Go trials. Ventral prefrontal and ACC activity were decreased in both ADHD groups to violations of identity (No-Go trials), as were cerebellar activations related to violations of stimulus timing. Thus, this study linked dysfunction within frontocerebellar circuits to impaired prediction of future events in ADHD, which likely accounts for the inability to prepare responses appropriately and to alter behavior in response to environmental contingencies.

In a similar approach to the identification of more fundamental components of ADHD-related decrements in executive function, Hale et al. [21] examined activation during forward and backward digit span tasks in a small adult sample (n = 12 per group; mean age ~ 35 and ~ 27 years in ADHD and HC groups, respectively). Adults with ADHD showed enhanced activation in areas related to phonological/verbal processing during both simple and complex working memory tasks, possibly reflecting increased demands on these processes during task performance. Divergent activations in areas such as superior parietal lobe and temporo-occipital cortex also were observed. However, the authors urge caution in interpretation because of the small sample size and several methodological flaws.

Konrad et al. [22] assessed specific aspects of attention: alerting, reorienting, and executive control. In 16 medication-naïve boys with ADHD and 16 HCs (all aged 8–12 years), behavioral deficits were observed only for executive control, whereas differential patterns of brain activation were observed for all aspects of attention, which the authors argue reflects a reliance on abnormal neural systems for attentional processing in ADHD. ADHD and HCs showed divergent patterns of activation in ACC, brainstem, inferior frontal gyrus (IFG) and insula, precentral gyrus, and putamen. Negative correlations between hyperactive/impulsive symptom severity and putamen activity were observed during both reorienting and executive control, implying that less severely affected children with ADHD were better able to activate the putamen in more attentionally demanding trials.

Medication-naïve participants also were studied by Pliszka et al. [23•], who found no significant differences between groups on any behavioral measures when comparing ADHD subgroups (eight medication naïve vs nine children medicated for at least 1 year, mean 4.9 years) and both groups with respect to 15 HCs (mean age of all groups ~ 13 years) during a stop signal task. Controls showed greater activation in an ACC region of interest (ROI) for incorrect relative to correct trials, whereas children with ADHD showed lower levels of activation and no significant difference between correct and incorrect trials. A similar pattern was observed in the left IFG/insula and less robustly in the right IFG/insula. The treatment and naïve groups differed only in the ACC; the treatment group did not differ between correct and incorrect trials, whereas the naïve group activated more for correct trials, the opposite pattern from controls. The authors suggest that when children with ADHD face increased demand (conflict/interference) or make an error, the ACC fails to activate appropriately and adjust cognitive control adequately to meet task demands. Error-related processing remains a relatively unexplored area of cognitive function in ADHD. One important next step to further our understanding of these results may be to investigate the potential role for error awareness in the group differences observed; studies (eg, [24]) have suggested that this meta-cognitive ability is a sensitive index of the integrity of executive control.

In search of genetically informative endophenotypes, Durston et al. [25•] examined the IFG during a Go/No-Go task in 11 children and adolescents with ADHD, 11 of their unaffected siblings, and 11 HCs (mean age ~ 14–15 years). Task difficulty was manipulated by parametrically varying the number of Go trials that preceded a No-Go (one, three, or five). Although errors increased as a function of the number of preceding Go trials, the only behavioral group difference was poorer accuracy for the ADHD group at the highest level of difficulty. During successful inhibitions, HCs activated bilateral IFG, ACC, middle frontal gyri (MFG) and superior frontal gyri, and

left IPL. Behavioral correlations suggested that activation in IFG was crucial to performance—HCs showed a positive relationship between activation in this area, and both increased difficulty and accuracy. Unaffected siblings showed similar correlations with difficulty and performance but overall lower levels of activation in IFG, MFG, and IPL. Children with ADHD also showed lower levels of activation in IFG, ACC, MFG, and IPL, and for them, activation in IPL correlated with performance, an observation consistent with reports of compensatory activation in ADHD during cognitive performance. The findings support the idea that the magnitude of activation in IFG during successful inhibition is sensitive to genetic vulnerability to ADHD.

Another proposed endophenotypic behavioral deficit in ADHD [26], increased intraindividual variability (IIV), has been examined in 30 typically developing children [27] aged 8 to 12 years using a simple Go/No-Go task in a rapid event-related design. Children with the highest response time (RT) coefficient of variation (CV; CV = RT SD/mean RT) made the most commission errors, supporting CV and an index of the efficiency of inhibitory control. CV and Go activation were negatively correlated in right anterior cerebellum but positively correlated in right PFC, caudate and posterior cerebellum, and left postcentral gyrus. No-Go activation was negatively correlated with CV in left presupplementary motor area, inferior parietal cortex, cerebellum, and right postcentral gyrus, whereas a positive correlation was found in right PFC and caudate. These findings were consistent with those in healthy adults [28] and suggested that more highly variable children are less efficient in inhibition and recruit higher-order regions to guide inhibitory control.

Studies of Resting State/Spontaneous-Intrinsic Activity

Investigating the brain's activity at rest provides a novel basis for examining individual differences in brain function [29]. Raichle et al. [30] first stimulated interest in resting state neural activity by describing a "default mode" network of brain regions that shows strongly coherent spontaneous activity at rest ("functional connectivity"), which is suppressed during performance of attention-demanding cognitive tasks. Task-based functional imaging studies of ADHD typically have neglected deactivations, which are characteristic of the default mode network. However, one group has been prolific in examining resting state functional connectivity in adolescents with ADHD. In a series of intriguing papers describing a range of analytical methods applied to a single dataset of 13 boys with ADHD and 12 controls [31–34], these authors have described between-group differences in resting state functional connectivity, finding decreases in the amplitude of the spontaneous low-frequency fluctuations that form the basis of connectivity of the default mode network. The same group reported increased functional connectivity between an ROI consisting of the entire dorsal ACC and widespread regions, including the thalamus, cerebellum, insula, and pons [32].

Given the vast literature implicating frontal regions in top-down control processes, their involvement in maintaining consistent behavioral performance is not surprising. However, the specific mechanism(s) by which frontal regions modulate IIV and attentional lapses remained poorly defined until a recent study of the relationship between IIV and the default mode network [35]. Weissman et al. [35] demonstrated that longer RTs, presumed to reflect momentary lapses in attention, were associated with failure to suppress activity in the default mode network. Decreased cue-related activation in three prefrontal regions (right middle frontal gyrus, right inferior frontal gyrus, and right dorsal ACC) predicted slower RTs and decreased default mode network suppression. This study provided the first demonstration of an association between activation in the default mode network and behavioral performance, and supported the links between momentary lapses in attention, IIV, and the strength of suppression of activity in regions supporting task-irrelevant processing, links that support the proposed investigations of IIV in ADHD.

In considering these links, a recent hypothesis paper [36] proposed that fronto-default mode interactions may represent a novel locus of dysfunction in ADHD, potentially accounting for ADHD-related increases in intrasubject variability. Initial support for this hypothesis is provided by an examination of resting state functional connectivity in 20 adults with ADHD (aged ~ 35 years) and 20 age- and sex-matched HCs (aged ~ 31 years) [37••]. This study tested for the presence of ADHD-related differences in functional connectivity between each of the three frontal foci identified by Weissman et al. [35]—dorsal ACC (dACC), right IFG (rIFG), and right MFG (rMFG)— and the default mode network. Although both rIFG and rMFG ROIs were significantly negatively related to precuneus and posterior cingulate cortex (collectively, retrosplenial complex [RSC]) in both groups, these relationships did not differ significantly. In contrast, functional connectivity analyses of the dACC ROI demonstrated significantly less negatively correlated activity ($P < 0.0004$) in precuneus and posterior cingulate cortex in subjects with ADHD. This initial application of resting state approaches to the examination of ADHD-related decreases in default mode network functional connectivity identified the dACC/RSC circuit implicated in IIV as a potential novel locus of dysfunction in ADHD.

Conclusions

In reviewing the recently published literature, several trends emerge. First, the pace and sophistication of neuroimaging studies in ADHD have increased dramatically

in the years following the Decade of the Brain. Second, although evidence in favor of frontal involvement in ADHD is considerable, other brain circuits outside of the frontal lobes are clearly implicated, and there is increasing interest in exploring potential loci of dysfunction outside the frontal lobes. Specifically, there has been a shift toward the identification of the neural correlates of potentially more fundamental lower-level deficits (eg, involving sensory and spatial processes) that can account for lower- as well as higher-order cognitive decrements. Third, a welcome development has been the imaging of medication-naïve samples, which can serve to alleviate concerns about the independence of observations from either long-term effects of medication or the acute effects of medication withdrawal. Fourth, investigators are beginning to contrast children, adolescents, and adults with ADHD across these developmentally distinct stages, which is crucial given the developmentally contingent nature of ADHD.

Finally, analysis of spontaneous-intrinsic brain activity during resting state holds great promise for overcoming some of the challenges of standard fMRI by bypassing confounding issues related to task performance while facilitating larger sample sizes and potential longitudinal follow-up studies. Additionally, functional connectivity mapping provides remarkably detailed information about interregional relationships in the brain. We predict that the insights provided by this innovative approach will yield fundamental insights into the neuropathophysiology of ADHD in the years to come.

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