Brain imaging of the neural systems affected in adults with attention-deficit/hyperactivity disorder


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A plethora of studies utilizing either anatomical or functional brain imaging have revealed differences between children and adolescents with attention-deficit/hyperactivity disorder (ADHD) and neurological normal individuals. However, relatively little research has examined patterns of brain activity in adults with ADHD. Such research is of interest because it can elucidate which aspects of the disorder are consistently observed across the lifespan. This article assesses the findings of a recently published study, which not only reported altered brain function in adults with ADHD during performance of an attentionally demanding response-inhibition task, but which also linked such alterations to the severity of ADHD symptomatology. These findings are discussed in relation to the growing number of studies examining alterations of neural function in adults with ADHD, as well as considerations of what information needs to be provided by neuroimaging before it can be successfully integrated into clinical practice.

Keywords: ADHD • functional magnetic resonance imaging • hyperactivity • impulsivity • inattention • neuroimaging • response inhibition • symptomatology

Attention-deficit/hyperactivity disorder (ADHD) is a developmental disorder characterized by the inability to sustain attention, increased distractibility, motor hyperactivity and impulsivity [1]. With regards to its neural basis, increasing evidence suggests that the disorder is characterized by alterations in fronto-striatal regions linked to dopaminergic function [2], as well as alterations in parietal and cerebellar regions [3]. A major question currently being addressed by researchers is what aspects of the disorder are consistently observed from childhood through adolescence and into adulthood. As it is becoming clear that important structural and functional changes occur in the brain during adolescence and young adulthood [4], determining which neural systems are affected by ADHD both during childhood and through adulthood is likely to identify those brain regions fundamental to the disorder.

Recently, a number of studies have examined which systems are affected in adults with ADHD (reviewed in [5]). One of these, by Schneider and colleagues, reviewed here, finds that the brain systems affected in adults with ADHD are similar to those altered in children and adolescents [6]. A brief synopsis of their paper follows.

Methods
Participants
Participants were adults, ranging in age from 18 to 45 years: 11 individuals with combined type ADHD that persisted from childhood through to adulthood (persistent group), nine individuals who met the full ADHD criteria during childhood but did not as adults although they still exhibited impairment (partially remitted group), and 17 control individuals. All ADHD individuals had a total score of 30 or more on the German-validated form of the Wender Utah Rating Scale [7] to ensure childhood onset of symptoms. Current ADHD symptoms were self-rated via a standardized and validated
self-rating scale for adults (ADHD Self-Rating Scale) [8], which consists of 18 items scored on a 0–3 Likert Scale, broken down in three subscales: inattention, impulsivity and hyperactivity. These symptoms scores were then correlated with brain activity.

**Functional brain imaging**

Brain activity was recorded via functional MRI (fMRI) while individuals performed a version of the continuous performance task, which was similar in design to the Go/No-go task. Individuals saw a series of pseudorandomized letters, presented for 420 ms each. They were instructed to press a button if the letter O was followed by the letter X (Go condition), but not by other letters (No-go condition). Within a sequence of 285 items, there were 30 Go events and 30 No-go events within a 12-min run. Focus was on the No-go condition, as it is thought to index inhibitory processes that are disrupted in ADHD.

**Image analysis**

A standard image analysis path was performed in SPM 99. Two-sample t-tests were performed comparing groups for the Go and No-go conditions separately. For each condition (Go, No-go), contrasts examined the continuous performance test task versus a control task, which was not specified (but which may have been other letters pairs within the sequence). The p-value was set at 0.001 (uncorrected) with a minimum cluster size of 5 voxels. For correlational analyses, the symptom rating was regressed against brain activation.

**Behavioral results**

**Symptoms**

Data indicated that the Wender Utah Rating Scale scores of the persistent and partially remitted ADHD patients did not differ, suggesting that their childhood levels of ADHD were similar. However, current symptoms were significantly higher in the persistent group compared with the partially remitted group and controls (Mann-Whitney test, Z = -3.4 and -4.4, respectively; p = 0.000). The mean IQ of the ADHD individuals (persistent = 106, partially remitted = 115) was lower than that of controls (mean = 126), so that brain imaging analyses were also performed with IQ as a covariate.

**Continuous performance test**

Patients with persistent ADHD made significantly more omission errors and had longer reaction times in the Go condition than controls. No other group differences in performance were significant.

**Brain imaging**

In healthy participants, a large network of brain structures including fronto-striatal-thalamic loops (involved in executive function and attentional control) was activated by the No-go condition, consistent with prior meta-analyses of this task [9].

Group comparisons were also performed. Compared with controls, ADHD individuals exhibited less activity in the right and left superior frontal gyri (BA 6 and 8), the right caudate, right supramarginal gyrus (BA 40) and left superior parietal lobe (BA 7). They also exhibited less activation in the right superior and middle temporal gyri, which were not significant after controlling for IQ. ADHD individuals exhibited greater activity in a variety of visual processing regions (fusiform and lingual gyri), with only the left fusiform gyrus remaining significant after controlling for IQ. Relatively few differences were found between persistent ADHD and remitted groups, and, as the authors note, these contrasts are underpowered.

**Correlations with symptoms**

In all cases, correlations were performed between symptoms and activation in the No-go condition.

**Inattention**

Higher inattention scores were associated with lower activation in frontal regions (BA 6 and 8) and parietal regions (BA 40 and 7), which are implicated in attentional control, as well as the caudate nucleus. Thus, these findings are consistent with a disruption in fronto-striatal circuitry as has been observed in children and adolescents with ADHD.

**Impulsivity**

Increased impulsivity was correlated with activity in lateral (BA 6 and 8) as well as medial (BA 32, dorsal anterior cingulate) prefrontal regions, and superior and inferior parietal regions (BA 7 and 40).

**Hyperactivity**

A similar pattern was observed for hyperactivity as for inattention – increasing scores were associated with decreased activation in frontal (BA 6 and 10) and parietal (BA 7) regions.

In all cases, higher symptomatology was associated with increased activity in visual processing regions, suggesting that increased symptoms may be associated with an inability to filter out sensory aspects of the stimuli.

**Discussion & significance**

On the basis of these findings, the authors conclude that similar brain networks are disrupted during adulthood in individuals with ADHD as occurs during childhood. The current study is consistent with a growing body of studies that have found alterations in brain activation in adults with ADHD during performance of a variety of tasks including those related to attention [10,11], task switching [12], working memory [13–17], sensorimotor timing [18], and reward anticipation and outcome [19,20]. Across these studies, the brain regions most consistently affected are prefrontal regions, the basal ganglia, parietal regions and often also the superior temporal gyrus, insula and cerebellum.

With regards to response inhibition per se, the pattern observed in the current study varies from other recent reports. For example, at least one study [21] found no differences in prefrontal brain activation in adults with ADHD and controls, but that the ADHD group demonstrated increased parietal activation. Another [22] found increased activation in the inferior frontal gyrus and putamen during response inhibition, and decreased activation during...
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feedback in inferior frontal/orbitofrontal regions, hippocampus, nucleus accumbens and caudate. This pattern varies from a consistent disruption of activity in the right inferior frontal gyrus in children with ADHD [23], as well as a recent report that the anatomical volume of this region in adults with ADHD predicts measures of response inhibition [24]. Hence, although there is some agreement about alterations in brain function in adults with ADHD during performance of tasks requiring response inhibition, the direction of those relationships (increased brain activation, decreased brain activation) remains unclear and may depend both on the population of individuals assessed and the nature of the task.

Probably more important and novel is the linkage of symptom severity to activity in particular brain regions. If neuroimaging is to have an impact on clinical practice, understanding the heterogeneous way in which ADHD manifests itself and the neural systems associated with such heterogeneity will likely be important. Because the authors observed a relationship with symptom severity, they posit that the study provides evidence that ADHD is a dimensional disorder, consistent with the other conceptualizations of this disorder as occurring along a spectrum [25]. The issue of using symptom severity in conjunction with brain imaging is an important one and discussed below in more detail.

The study also demonstrated a somewhat different relationship of symptom severity and brain activity across the three main types of symptoms: inattention, impulsivity and hyperactivity. Whereas the regions implicated in inattention and hyperactivity were similar, those regarding impulsivity were somewhat different, most notably correlating with activity in the anterior cingulate cortex, which has been proposed to be a major region disrupted in ADHD [26].

Despite the intriguing pattern of results obtained in this study, they should probably be viewed with some caution. The reported results are uncorrected for multiple comparisons and the cluster size threshold is small. Furthermore, inspection of the data tables indicates that the cluster sizes are generally less than 50 voxels. As such, it will be important for the current results to be replicated.

In addition, the study leaves open the question of how specific the observed relationship between brain systems and different symptom subgroups are. Although the pattern of correlations between symptom severity and brain regions varies somewhat for inattention and hyperactive symptoms, a direct test for differences or commonalities was not performed. To investigate this issue in more detail, future researchers will likely need to consider which brain regions correlate with overall symptom severity, and then which are specific to each of the main subgroups of symptoms through partial correlations or some other statistical technique.

Expert commentary

One of the more important (and novel) issues raised by the reviewed study is how symptom severity relates to patterns of brain activation. This study employed the approach of regressing symptom severity scores across individuals against the level of localized brain activity. It should be noted that the use of correlations between brain activation as assessed by fMRI and behavioral variables has been controversial as of late (e.g., [27,28]). Considering the low p threshold and small clusters size observed, it is not clear to which the current findings will replicate. Nonetheless, recent evidence from our own laboratory [29] suggests that correlating symptom severity with functional brain activation may hold much promise for understanding the underlying brain systems affected in ADHD. In our study we correlated symptom severity in young adults with ADHD who were not comorbid for any other psychiatric disorder or learning disability with brain activation during different conditions of the Stroop task (incongruent, congruent and neutral) compared with a fixation baseline. We identified regions that consistently showed an association with symptom severity across all three conditions (as a way to protect against false-positive findings). Unlike the findings of Schneider and colleagues, the regions identified were not limited to those that were identified as having reduced activity within the ADHD group as compared with controls. As a result, we have proposed that regions that reveal group differences may be those that are consistently affected across all ADHD individuals, whereas those that show correlations with symptom severity may reflect multifactorial influences that reflect the heterogeneity in the manner in which ADHD manifests across individuals. The regions linked to symptom severity can be roughly grouped into cortico-striatal-thalamic loops, as well as cerebellar-thalamo-cortical loops.

Analyses involving symptom severity are often limited to a clinical group because control individuals typically show few symptoms. The nonoverlapping distribution between the clinical and control groups can make it difficult to know whether constructs associated with symptom severity, such as brain activation, are specifically linked to the clinical disorder. For example, greater inattention may be linked to less activity in prefrontal cortex for all individuals, regardless of whether or not one meets criteria for ADHD. In consideration of this issue, we examined whether patterns of activity within the brain regions associated with ADHD symptom severity differed for ADHD and controls [29]. We found that the variability of fMRI signal over time (i.e., over the duration of the task) in regions linked to symptom severity was greater for ADHD individuals than controls, but that such group differences were not observed for regions whose activity was not associated with symptom severity, such as visual processing regions. Furthermore, the variability of the fMRI signal over time in these regions was related to behavioral response variability, one of the cardinal cognitive symptoms of ADHD [30]. Hence, these additional analyses provide converging evidence that the regions linked to the severity of symptoms are relevant to the manifestation of the disorder.

The current study identified fronto-striatal-thalamic and fronto-parietal networks as being affected in adults with ADHD. This finding is consistent with discussions of a number of altered brain circuits in this disorder [31]. As such, in the future it may be that our understanding of the neural disruptions in ADHD will be advanced more not by searching for disruptions in activity in particular brain regions (as discussed above), but rather by alterations in the relationship between brain regions, either anatomically or functionally. Recent evidence from studies on adults with ADHD suggests that this may be a fruitful approach. For example, alterations have been observed in functional connectivity in adults with ADHD during both cognitive processing,
such as during the performance of WM tasks [15], and also during resting state [32]. Also reported are differences in anatomical connectivity, as evidenced by white matter integrity [33,34] and callosal structure [Hutchinson AD, Mathias JL, Jacobson BL et al. Corpus callosum size and integrity in young adults with combined-type attention deficit/hyperactivity disorder. Psychiatry Res. (Manuscript Submitted)]. In conclusion, a systems-level, rather than a strictly localizationist approach, may prove to be more informative in revealing the etiology of ADHD (reviewed in [35]).

Finally, it may be that ADHD is characterized not only by alterations in the neural systems that support cognitive abilities compromised in ADHD, such as executive function, timing, working memory and sensorimotor integration, but also by alterations in the so-called default network, which appears to become active when cognitive processing is low [36]. Our laboratory has found that decreases in default-network activity are reduced in ADHD individuals in the face of cognitive demand [Banich MT, Burgess GC, Depue BE et al. Activity in the attentional and default networks in young adults with combined-type attention deficit hyperactivity disorder during attentional demand. Brain Res. (Manuscript Submitted)], consistent with that reported in children [37].

Five-year view

The issue of how neuroimaging will impact psychiatric diagnosis and treatment of ADHD, as well as other psychiatric disorders, is one that will be highly relevant for years to come. Although functional neuroimaging is providing new insights into the neural basis of ADHD in adulthood, there remains a long way to go before such information will be useful in a clinical setting. One requirement will be to clearly identify the neural systems involved and to have tasks that will engage those systems so that dysregulation can be identified. A second step will be to determine how alterations in those systems are related to symptom severity and/or subtypes. Whether symptom severity is just reflected in the degree of altered activity in regions that distinguish ADHD from control individuals, or whether symptom severity engages a more broad-based set of regions as we have observed [29], will be a question for future research. Finally, if brain imaging is to have diagnostic value, it will require that there is a specific brain signature that identified ADHD as distinct from many other psychiatric disorders that affect prefrontal cortex and/or involve dopaminergic transmission (e.g., bipolar disorder and schizophrenia).

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Key issues

- The degree to which the neural systems affected in adults with attention-deficit/hyperactivity disorder are similar to those observed in children and adolescents with the disorder remains to be clarified. The current study suggests that there is some developmental continuity to the systems affected.
- Whether distinct brain systems are related to specific ADHD symptoms (e.g., inattention, hyperactivity and impulsivity) in adulthood remains to be seen. The current study raises the possibility that different symptoms indeed may be dependent on distinct neural systems.
- If neuroimaging is to impact the diagnosis and treatment of ADHD, these two issues will need to be clarified, as well as the ability to ascertain how the brain systems affected in ADHD are distinct from alterations observed in other psychiatric disorders.

References

Papers of special note have been highlighted as:

• of interest
** of considerable interest


** Excellent review of current thinking regarding brain systems that are affected in individuals with attention-deficit/hyperactivity disorder (ADHD).


• A recent review of findings related to brain imaging in adults with ADHD.


Another paper showing a relationship between symptom severity and brain activation in adults with ADHD, which also demonstrates the specificity of the identified brain regions as well as their relationship to behavioral performance.


Recent review of altered connectivity between brain regions in individuals with ADHD.


Fassbender C, Zhang H, Buzy WM et al. A lack of default network suppression is linked to increased distractibility in ADHD. Brain Res. 1273, 114–128 (2009).