

The neural correlates of attention deficit hyperactivity disorder: an ALE meta-analysis

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Background: Attention deficit/hyperactivity disorder (ADHD) is one of the most prevalent and commonly studied forms of psychopathology in children and adolescents. Causal models of ADHD have long implicated dysfunction in fronto-striatal and frontal-parietal networks supporting executive function, a hypothesis that can now be examined systematically using functional neuroimaging. The present work provides an objective, unbiased statistically-based meta-analysis of published functional neuroimaging studies of ADHD. **Methods:** A recently developed voxel-wise quantitative meta-analytic technique known as activation likelihood estimation (ALE) was applied to 16 neuroimaging studies examining and contrasting patterns of neural activity in patients with ADHD and healthy controls. Voxel-wise results are reported using a statistical threshold of $p < .05$, corrected. Given the large number of studies examining response inhibition, additional meta-analyses focusing specifically on group differences in the neural correlates of inhibition were included. **Results:** Across studies, significant patterns of frontal hypoactivity were detected in patients with ADHD, affecting anterior cingulate, dorsolateral prefrontal, and inferior prefrontal cortices, as well as related regions including basal ganglia, thalamus, and portions of parietal cortex. When focusing on studies of response inhibition alone, a more limited set of group differences were observed, including inferior prefrontal cortex, medial wall regions, and the precentral gyrus. In contrast, analyses focusing on studies of constructs other than response inhibition revealed a more extensive pattern of hypofunction in patients with ADHD than those of response inhibition. **Conclusions:** To date, the most consistent findings in the neuroimaging literature of ADHD are deficits in neural activity within fronto-striatal and fronto-parietal circuits. The distributed nature of these results fails to support models emphasizing dysfunction in any one frontal sub-region. While our findings are suggestive of the primacy of deficits in frontal-based neural circuitry underlying ADHD, we discuss potential biases in the literature that need to be addressed before such a conclusion can be fully embraced. **Keywords:** Attention deficit/hyperactivity disorder (ADHD), meta-analysis, neuroimaging, functional magnetic resonance imaging (fMRI), positron emission tomography (PET), executive function.

Models of attention-deficit/hyperactivity disorder (ADHD) have long posited that a core deficit in frontal lobe function underlies its various cognitive and behavioral manifestations. In particular, fronto-striatal and fronto-parietal networks supporting an array of top-down or executive processes, such as dorsolateral prefrontal cortices, anterior cingulate cortices, and associated striatal regions, are frequently cited as loci of dysfunction in ADHD (e.g., Barkley, 1997; Castellanos & Tannock, 2002). Until recently, such models have relied heavily upon anatomical and neuropsychological studies of ADHD (see recent reviews, Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005; Seidman, Valera, & Makris, 2005) as well as inferences based upon functional neuroimaging findings from healthy normal adults. However, with recent advances in non-invasive neuroimaging techniques such as functional magnetic resonance imaging (fMRI), researchers have begun examining the neural correlates of ADHD, resulting in a rapidly growing literature.

Given both the strong association between executive function and the frontal lobes, and the substantial literature confirming the presence of executive dysfunction in ADHD (Willcutt et al., 2005), it is not surprising that nearly all neuroimaging studies have focused on cognitive paradigms assessing executive processes. Amongst these, response inhibition has been the most studied of executive top-down functions, reflecting the impact of an influential theory which posited inhibitory dysfunction as the primary deficit in ADHD (Barkley, 1997).

Several recent reviews have examined the ADHD neuroimaging literature. Bush, Valera, and Seidman (2005) surveyed over a dozen neuroimaging studies of ADHD, encompassing a variety of functional imaging techniques (PET, SPECT, fMRI, EEG) and cognitive paradigms (e.g., inhibitory control, selective attention, working memory, and vigilance). They found a consistent pattern of frontal dysfunction with altered patterns of activity in anterior cingulate, dorsolateral prefrontal, and ventrolateral prefrontal cortices, as well as associated parietal, striatal, and cerebellar regions. Despite broad consistencies,

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Bush et al. noted multiple challenges in comparing results across studies, and cited difficulties in interpretation due to small sample sizes and methodological issues related to statistical correction for multiple comparisons that impact rates of false positives and false negatives.

Aron and Poldrack (2005) examined the existent literature with a narrower focus on the neural correlates of inhibitory control rather than the broader construct of executive processes. Their review included imaging, behavioral, and genetic studies in patients with ADHD as well as healthy participants, along with basic animal studies. Their conclusions support the hypothesis that dysfunctions in prefrontal cortex (specifically the right inferior prefrontal cortex), basal ganglia, and the related neurotransmitter systems (dopaminergic, noradrenergic, and serotonergic) underlie inhibitory deficits in ADHD.

Here we build upon these prior efforts by using the recently developed activation likelihood estimation (ALE) (Lancaster, Laird, Fox, Glahn, & Fox, 2005; Laird et al., 2005a) technique to carry out a quantitative voxel-wise meta-analysis of published functional neuroimaging studies of ADHD. While prior reviews have attempted to synthesize the literature, a quantitative meta-analysis can provide a useful method to assess the state of the field, and to provide a plan for future research, for several reasons. First, quantitative meta-analytic techniques provide an objective, unbiased, statistically-based approach to examine findings across studies, as opposed to the traditional 'box-score' or label-based qualitative methods (Laird et al., 2005b). Second, a voxel-wise approach provides increased spatial resolution, delineating not only large frontal sub-regions but specific areas within them by optimally using data generated across functional imaging studies. The advantages of increased spatial distinction are substantial in the frontal lobes given the remarkable functional heterogeneity that is increasingly being mapped at the level of sub-lobar regions (Stuss, Murphy, Binns, & Alexander, 2003; Miller & Cohen, 2001; Wagner, 1999). Finally, a quantitative meta-analysis yields specific brain coordinates that are confirmed across multiple studies, thus helping to filter out otherwise unavoidable spurious activations representing type I errors.

It is important to note that this is a novel application of the ALE meta-analytic methodology. Typically, researchers have used ALE to examine a particular cognitive construct across a set of studies within a relatively homogenous population (e.g., healthy adult volunteers) (Laird et al., 2005a, 2005b). Here, we use ALE to examine differences associated with ADHD across a set of studies assessing executive function. Ideally, a separate meta-analysis would be conducted for each individual executive process as it relates to ADHD. However, given the infancy of the current literature, with

the exception of response inhibition, this is not possible, as no individual construct has a sufficient number of studies to date. Instead, it is more practical to study the commonalities across executive function tasks in a systematic statistically driven fashion, with the realization that some regions specific to an individual executive process may have decreased detectability using this method. Support for this approach comes from the descriptive reviews already discussed (Aron & Poldrack, 2005; Bush et al., 2005), which noted a pattern of ADHD-related hypofunction in specific frontal regions (e.g., anterior cingulate cortex) across studies in the existent literature, despite the heterogeneity of methods. Given the large number of studies examining response inhibition in ADHD, we carried out a second meta-analysis focusing on this construct alone.

One potential difficulty for a meta-analysis of neuroimaging in ADHD is that about a third of current studies do not provide direct comparisons between patients with ADHD and healthy controls. Instead, those studies have typically reported activations for each group (ADHD, control) individually, with qualitative assessments about differences in the patterns observed for the two individual groups. Alternatively, some studies have simply presented region of interest analyses. Furthermore, the small sample sizes included in several of the studies reporting direct comparisons may limit their ability to detect group differences. An important advantage of the ALE approach is that we can overcome these obstacles to some degree by carrying out separate meta-analyses for each group (ADHD, controls) and then comparing the two meta-analyses statistically.

Methods

Study selection

Neuroimaging studies comparing patterns of activity in patients with ADHD and healthy comparisons were found primarily by searching the PUBMED database (<http://www.pubmed.org>) and Google Scholar (<http://scholar.google.com/schhp?hl=en&tab=ws&q=>) using the keywords: ADHD, fMRI, PET, Executive Function, Inhibition, Working Memory, Child, Adolescent, Adult, and Imaging. We then reviewed the reference lists of each of these articles to obtain additional papers. Four additional articles were included after the initial review process. Three articles currently in press at the *American Journal of Psychiatry* were provided by the editor with the permission of the authors, and one article that had not appeared during our database searches was pointed out by an anonymous reviewer. Only articles that reported activation foci as 3-D coordinates (x, y, z) in stereotactic space, examined active cognitive constructs, and presented results for individual participant groups were included. The 16 studies identified using our criteria are listed in Table 1. These studies yielded a total of 134 foci of activation for patients with ADHD and 180 foci of activation for controls. For the purpose of analysis, any foci that were reported according to the

Table 1 Data sources

Article	Imaging modality	N	Task(s)	Contrast(s)
Booth et al., 2005	fMRI (1.5T)	12 ADHD 12 Controls	Visual search; Go-No go	Nine stimuli vs. one stimulus; No-go vs. Go
Bush et al., 1999	fMRI (1.5T)	8 ADHD 8 Controls (adults)	Counting Stroop	Interference vs. neutral
Durstun et al., 2003	fMRI (1.5T)	7 ADHD 7 Controls	Go-No go (Modified)	No-go vs. Go
Ernst et al., 2003	PET	10 ADHD 12 Controls (adults)	Decision-making gambling task	Choice vs. No choice
Pliszka et al., in press	FMRI (2.0T)	17 ADHD 15 Controls	Stop task	Stop vs. Go; Successful stop vs. Unsuccessful stop
Rubia et al., 2005	FMRI (1.5T)	16 ADHD 21 Controls	Stop task	Stop vs. Go
Schulz et al., 2004	FMRI (1.5T)	10 ADHD 9 Controls	Go-No go	No-go vs. Go
Schulz et al., 2005	FMRI (1.5T)	8 ADHD 8 Controls	Stimulus and response Conflict tasks	Stimulus conflict vs. control and location; Response conflict vs. control; Combined conflict condition vs. control and location
Schweitzer et al., 2000	PET	6 ADHD 6 Controls (adults)	Paced auditory Serial addition task	Serial addition vs. Random number vocalization
Schweitzer et al., 2004	PET	10 ADHD 11 Controls (adults)	Paced auditory Serial addition task	Serial addition vs. Random number vocalization
Silk et al., 2005	FMRI (3.0T)	7 ADHD 7 Controls	Mental rotation	Mental rotation vs. Fourier-transformed noise patch
Smith et al., in press	FMRI	19 ADHD 27 Controls	Go-No go Motor-Stroop Switch task	No-go vs. oddball trials; Incongruent vs. congruent; Switch vs. Repeat trials
Tamm et al., 2004	FMRI (1.5T)	10 ADHD 12 Controls	Go-No go (modified)	No-go vs. Go
Tamm et al., in press	FMRI (1.5T)	14 ADHD 12 Controls	Oddball task	Oddball vs. Standard stimulus
Vaidya et al., 2005	FMRI (3.0T)	10 ADHD 10 Controls	Eriksen Flanker + Go-No go	Incongruent vs. Neutral; No-go vs. Neutral
Valera et al., 2005	FMRI (1.5T)	20 ADHD 20 Controls (adults)	N-Back	2-back vs. 'X' vigilance task

These studies contained a total of 134 foci of activation for patients with ADHD and 180 foci for controls. Unless specifically noted above as 'adults', study participants were children and adolescents.

atlas of the Montreal Neurological Institute (MNI coordinates) were converted to Talairach coordinates using the algorithm implemented by Matt Brett (<http://www.mrc-cbu.cam.ac.uk/Imaging/Common/downloads/MNI2tal/mni2tal.m>). Of the ten functional neuroimaging studies of ADHD not included in this meta-analysis, six studies were excluded because they did not provide stereotactic coordinates (Ernst et al., 1994; Vaidya et al., 1998; Sunshine et al., 1997; Zang et al., 2005; Rubia et al., 2001; Teicher et al., 2000), one contained no active cognitive task (Ernst, Cohen, Liebenauer, Jons, & Zametkin, 1997), three examined only effects of medication treatment rather than effects of cognitive tasks (Anderson, Polcari, Lowen, Renshaw, & Teicher, 2002; Teicher et al., 2000; Schweitzer et al., 2003), and a final study was excluded from analyses because results were not reported for individual participant groups (Rubia et al., 1999).

Meta-analytic techniques

All meta-analyses were carried out using the activation likelihood estimation (ALE) technique (Turkeltaub, Eden, Jones, & Zeffiro, 2002) implemented in BrainMap (Laird et al., 2005a). Based on the Talairach stereotactic coordinates reported by the studies listed in Table 1,

two separate meta-analyses were conducted, one using the foci reported for patients with ADHD and one using the foci reported for controls. More specifically, for each group, activation likelihood estimates were calculated for each voxel by modeling each coordinate with an equal weighting using a 3-D Gaussian probability density function with FWHM = 10 mm. We next carried out a permutation test to determine the voxel-wise significance of the resulting ALE values. We made use of a non-parametric statistical approach previously described by Turkeltaub et al. (2002), in which 5000 permutations were generated using the same number of foci and FWHM as used to generate the ALE map. As such, no assumptions were made with respect to the distribution or spatial separation of these random foci (Laird et al., 2005a; Turkeltaub et al., 2002). Resulting statistical maps were corrected for multiple comparisons using false discovery rates (FDR), and then thresholded at $p < .05$, corrected, with a cluster extent threshold of 16 voxels. To directly compare patients with ADHD and controls, we used the ALE maps generated for each group to calculate ALE difference maps, controls - ADHD and ADHD - controls. Each of these difference maps was entered into a permutation analysis to generate voxel-wise statistical scores, as was previously done for the individual meta-analyses.

Given the existence of a sufficient number of studies to examine response inhibition specifically, we carried a second set of meta-analyses (ADHD only, controls only, controls – ADHD, ADHD – controls) using the same approach, but only included those studies examining response inhibition (Go No-go and Stop Tasks). To more fully measure the effect of response inhibition on the overall meta-analysis, we also created meta-analyses using those tasks excluded from the response-inhibition meta-analyses.

Finally, to examine other possible sources of heterogeneity, additional separate meta-analyses were carried out for the studies that included only child and adolescent participants (11 studies) and the studies that only included medication-naïve participants (four studies).

Results

Controls only

Consistent with current models of executive function and prior work using the specific tasks selected by ADHD investigators, our meta-analysis detected significantly elevated probabilities of activation in a distributed network of brain regions both in frontal and posterior regions (see Table 2 and Figure 1). Frontal regions showed significantly elevated probabilities of activation in areas of anterior cingulate cortex (BA 32, BA 24), left dorsolateral prefrontal cortices (DLPFC)(BA 6, BA 8), and bilateral inferior prefrontal cortices (BA 13, BA 45). Additionally, significantly elevated probabilities of activation were identified in right-sided thalamus, claustrum, insular cortex (BA 13), and striatum, as well as bilateral sub-regions of parietal lobe (bilateral BA 7, right BA 40). An area of left occipital cortex (BA 19) was also shown to have a significantly elevated probability of activation.

ADHD only

For patients with ADHD, similar to controls, our meta-analysis demonstrated a distributed pattern of regions with significantly elevated probabilities of activation (see Table 2 and Figure 1). With the exception of two large clusters in the left middle frontal gyrus, these clusters were generally smaller and distributed over fewer structures than the clusters identified in the ALE maps from controls. Frontal regions showed significantly elevated probabilities of activation in areas of bilateral middle frontal gyrus, and left medial frontal lobe (bilateral BA 10, left BA 46, and right BA 6). Activations in anterior cingulate were particularly inconsistent, with no cluster reaching significance. Significantly elevated probabilities of activation in ventral prefrontal cortices were much more prominent in the left hemisphere, unlike in controls where they were detected bilaterally. Significantly elevated probabilities of activation were detected in thalamus bilaterally

ally and in the lentiform nucleus (portions of putamen and globus pallidus) only on the right. A significantly elevated probability of activation was also noted in the posterior cerebellum on the right which extended to the occipital lobe of patients with ADHD.

Controls>ADHD

Consistent with models of hypofrontality, when the individual ALE maps for the two groups (ADHD, control) were compared statistically, controls demonstrated significantly greater probability of activation in a variety of regions relative to patients with ADHD, including bilateral areas of frontal lobe as well as areas of parietal lobe, and parts of striatum (see Table 2 and Figure 1). More specifically, areas of left ventral prefrontal cortex and DLPFC (BA 6, BA 8, BA 13, BA 44), anterior cingulate cortex (BA 24, BA 32), bilateral parietal lobe (bilateral BA 7, right BA 40), right thalamus, and left middle occipital gyrus (BA 19) showed a significantly greater probability of activation in controls than in patients with ADHD. There was also a significantly greater probability of activation in controls compared with patients with ADHD in an area centered at the right claustrum, covering 133 voxels, extending from insula (BA 13) to striatum (see Figure 1).

ADHD>Controls

A few regions had a greater probability of activation in patients with ADHD than in controls (see Table 2). Within the left frontal lobe, greater probabilities of activation were detected for insular cortex (BA 13) and portions of middle frontal gyrus (BA 9, BA 10). There was also an increased probability of activation in the left thalamus and the right paracentral lobule (BA 5).

Medication-naïve patients only

Of the 16 studies included in our meta-analyses, four examined the neural correlates of ADHD in medication-naïve patients (Pliszka et al., in press; Rubia, Smith, Brammer, Toone, & Taylor, 2005; Silk et al., 2005; Smith, Taylor, Brammer, Toone, & Rubia, in press). Though not uncommon in the study of psychiatric illness, the decision to include patients with a history of prior psychotropic medication treatment can limit a study's ability to definitively attribute group-differences to the underlying psychopathology as opposed to past effects of treatment. In order to gain some insight into the likelihood that our findings could reflect past treatment with psychotropic medications as opposed to ADHD, we carried out an exploratory meta-analysis limited to the four studies examining ADHD in medication-naïve patients. Though drastically less robust due to small sample size, we once again noted a pattern of

Table 2 Individual groups and group differences: all studies. Group differences: medication-naïve participants. Regions of significant elevated probability of activation

	x	y	z	Cluster size (voxels)	<i>p</i> *
Controls only					
Frontal lobe					
Inferior frontal gyrus (BA 45)(L)	-48	17	4	143	9.4×10^{-3}
Middle frontal gyrus (BA 8)(L)	-34	17	46	74	9.4×10^{-3}
Insula (BA 13)(L)	-34	25	13	65	8.5×10^{-3}
Middle frontal gyrus (BA 6)(L)	-24	-1	43	44	9.8×10^{-3}
Insula (BA 13)(L)	-40	-17	-7	34	8.2×10^{-3}
Middle frontal gyrus (BA 8)(L)	-40	28	38	24	7.7×10^{-3}
Insula (BA 13)(R)	42	15	6	19	8.0×10^{-3}
Medial wall					
Cingulate gyrus (BA 32)(L)	-4	22	37	370	9.5×10^{-3}
Cingulate gyrus (BA 24)(L)	-6	1	47	105	1.1×10^{-3}
Parietal lobe					
Precuneus (BA 7)(L)	-24	-53	51	191	1.0×10^{-3}
Parietal lobe (BA 40)(R)	28	-41	54	88	9.3×10^{-3}
Postcentral gyrus (BA 40)(R)	60	-21	19	42	8.8×10^{-3}
Superior parietal lobule (BA 7)(R)	26	-65	45	25	8.1×10^{-3}
Basal ganglia/thalamus					
Clastrum(striatum/insula)(R)**	26	19	0	238	9.9×10^{-3}
Thalamus (R)	22	-28	1	76	8.8×10^{-3}
Occipital lobe					
Middle occipital gyrus (BA 19)(L)	-46	-60	-6	25	8.1×10^{-3}
ADHD only					
Frontal lobe					
Middle frontal gyrus (BA 46)(L)	-40	14	20	827	9.9×10^{-3}
Middle frontal gyrus (BA 10)(L)	-34	46	12	216	7.7×10^{-3}
Middle frontal gyrus (BA 6)(R)	36	3	38	77	8.1×10^{-3}
Medial frontal lobe (BA 10)(L)	-16	47	-6	23	7.0×10^{-3}
Middle frontal gyrus (BA 10)(R)	36	38	5	17	6.9×10^{-3}
Parietal lobe					
Paracentral lobule (BA 5)(R)	12	-34	48	62	8.6×10^{-3}
Precuneus (BA 7)(C)	0	-55	44	37	8.4×10^{-3}
Inferior parietal lobule (BA 40)(L)	-34	-47	45	24	7.7×10^{-3}
Basal ganglia/thalamus					
Thalamus (L)	-12	-12	14	129	9.2×10^{-3}
Thalamus (R)	24	-24	13	63	7.3×10^{-3}
Lentiform nucleus (R)	10	3	1	40	7.7×10^{-3}
Cerebellum					
Cerebellum posterior, declive (R)	36	-64	-15	141	8.1×10^{-3}
Controls>ADHD					
Frontal lobe					
Precentral gyrus (BA 44)(L)	-50	15	6	73	9.5×10^{-3}
Middle frontal gyrus (BA 8)(L)	-34	17	46	65	9.4×10^{-3}
Middle frontal gyrus (BA 6)(L)	-24	-1	43	54	9.3×10^{-3}
Inferior frontal gyrus (BA 13)(L)	-34	27	12	18	8.2×10^{-3}
Medial wall					
Cingulate gyrus (BA 32)(L)	-4	24	33	262	9.6×10^{-3}
Cingulate gyrus (BA 24)(L)	-6	1	47	92	1.0×10^{-2}
Parietal lobe					
Precuneus (BA 7)(L)	-26	-53	53	121	1.0×10^{-2}
Parietal lobe (BA 40)(R)	30	-41	54	77	9.2×10^{-3}
Postcentral gyrus (BA 40)(R)	58	-21	19	32	8.6×10^{-3}
Superior parietal lobule (BA 7)(R)	26	-65	45	21	1.0×10^{-4}
Basal ganglia/thalamus					
Thalamus (R)	22	-30	-1	37	8.6×10^{-3}
Clastrum(striatum/insula)(R)**	26	19	0	133	8.9×10^{-3}
Occipital lobe					
Middle occipital gyrus (BA 19)(L)	-46	-60	-6	26	7.9×10^{-3}
ADHD>Controls					
Frontal lobe					
Insula (BA 13)(L)	-40	14	17	293	1.0×10^{-2}
Middle frontal gyrus (BA 9)(L)	-42	9	35	30	8.6×10^{-3}
Middle frontal gyrus (BA 10)(L)	-38	42	8	30	8.4×10^{-3}
Middle frontal gyrus (BA 9)(L)	-32	20	33	21	9.0×10^{-3}
Parietal lobe					
Paracentral lobule (BA 5)(R)	12	-32	50	38	9.2×10^{-3}

Table 2 Continued

	x	y	z	Cluster size (voxels)	<i>p</i> *
Basal ganglia/thalamus					
Thalamus (L)	-12	-14	13	35	9.3×10^{-3}
Studies of medication-naïve participants only:					
Controls>ADHD					
Frontal lobe					
Insula (BA 13)(R)	42	15	6	73	6.6×10^{-3}
Medial frontal gyrus (BA 10)(R)	18	59	-5	18	5.5×10^{-3}
Precentral gyrus (BA 4)(L)	-54	-11	27	17	5.7×10^{-3}
Medial wall					
Cingulate gyrus (BA 32)(L)	-2	26	27	17	5.5×10^{-3}
Medial frontal gyrus (BA 10)	0	59	-7	17	5.5×10^{-3}
Parietal lobe					
Postcentral gyrus (BA 40)(R)	60	-22	17	83	7.4×10^{-3}
Inferior parietal lobule (BA 40)(L)	-48	-44	42	18	5.7×10^{-3}
ADHD>Controls					
Frontal lobe					
Middle frontal gyrus (BA 9)(L)	-38	16	22	179	6.7×10^{-3}
Medial frontal gyrus (BA 10)(L)	-16	47	-6	71	6.1×10^{-3}
Temporal lobe					
Fusiform gyrus (BA 37)(R)	42	-58	-10	20	6.0×10^{-3}

BA = Brodmann area, L = left, R = right, cluster threshold = 16 voxels.

*False Discovery Rate (FDR) corrected *p* values.

**Area centered at claustrum extended from striatum to insula.

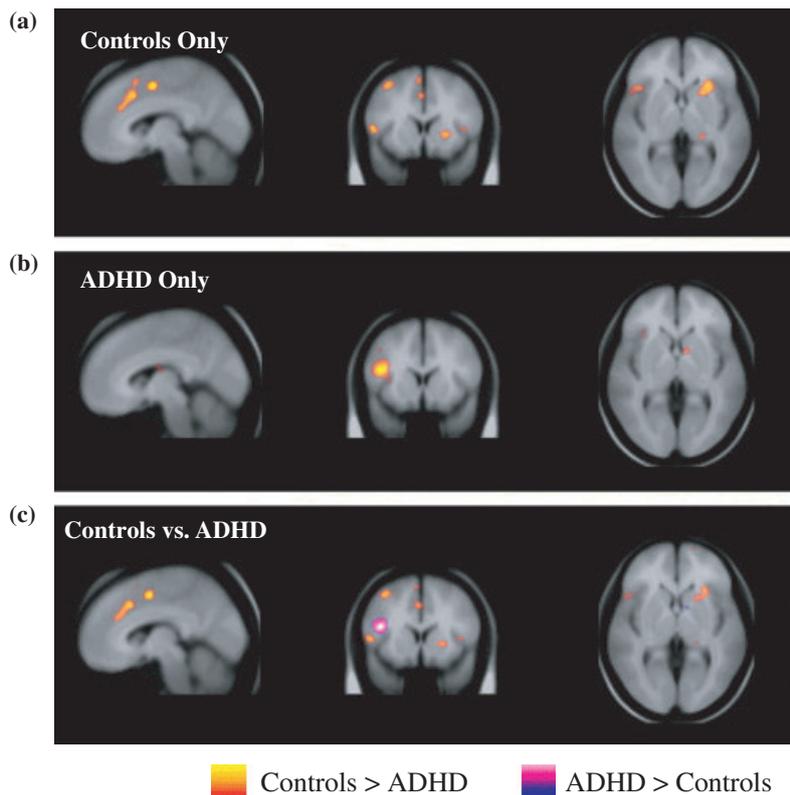


Figure 1 ALE meta-analyses across studies of ADHD and controls (a) Activation likelihood estimation (ALE) meta-analyses revealed an extensive pattern of significantly elevated probabilities of activation in regions of frontal lobe (bilaterally), medial wall, and right-sided striatum for Controls. (b) Patients with ADHD show more localized areas of significantly elevated probabilities of activation, predominantly in left frontal lobe. (c) To better compare the groups, a difference map of results for Controls vs. patients with ADHD is shown. For all images: *x* = -6, *y* = 13, *z* = 1 respectively, *p* < .05 corrected

significantly greater likelihood of activation in frontal and parietal regions for controls than patients with ADHD (see Table 2). Similar to our prior analyses, we

also noted a pattern of greater likelihood of activation in some left prefrontal regions for patients with ADHD relative to controls. As such, the medication-

naïve only analysis does not support the notion that our findings in the primary meta-analyses reflect the impact of medications as opposed to ADHD. Admittedly, caution should be taken in interpreting the findings of the medication-naïve meta-analysis, as the low number of studies ($n = 4$) clearly limits our ability to detect group differences and potentially decreases the stability of the findings.

Response inhibition only

In ALE meta-analyses generated using only studies that specifically examined response inhibition, a more restricted pattern of increased likelihood of activations was seen for controls compared to subjects with ADHD in the prefrontal cortices bilaterally (left BA 47 and BA 6, right BA 44), cingulate cortex (BA 24), left parietal lobe (BA 7), and right caudate (see Table 3). There were only two areas in which ADHD subjects had significantly more likely activa-

tions than controls, the medial frontal gyrus (BA 10) and the right paracentral lobule (BA 5).

Executive processes excluding response inhibition

ALE meta-analyses generated by excluding those studies examining response inhibition specifically revealed a pattern of increased likelihood of activations seen for controls compared to subjects with ADHD which mirrored the results from the meta-analyses of the total combined studies except for a lack of significantly greater likelihood of activation in the right inferior frontal lobe (a complete table of results for this subset of analyses is available upon request from the corresponding author). Controls were significantly more likely to have activations in areas of the left frontal lobe (BA 8, BA 9, BA 13), cingulate cortex (BA 10, BA 24, BA 32), bilateral parietal lobe (bilateral BA 7, right BA 5, left BA 3), right lentiform nucleus, right thalamus, as well as

Table 3 Individual groups and group differences: response inhibition only. Regions of significant elevated probability of activation

	x	y	z	Cluster size (voxels)	p*
Controls only					
Frontal lobe					
Inferior frontal gyrus (BA 47)(L)	-44	19	2	104	6.8×10^{-3}
Precentral gyrus (BA 6)(L)	-38	1	34	77	6.0×10^{-3}
Insula (BA 13)(R)	42	15	6	65	6.7×10^{-3}
Insula (BA 13)(L)	-42	6	17	53	6.2×10^{-3}
Medial wall					
Cingulate (BA 32)	0	12	35	18	5.9×10^{-3}
Basal ganglia/striatum					
Caudate (R)	14	2	23	37	6.0×10^{-3}
ADHD only					
Frontal lobe					
Paracentral lobule (BA 5)(R)	12	-34	49	140	7.2×10^{-3}
Insula (BA 13)(L)	-38	12	19	57	6.3×10^{-3}
Inferior frontal gyrus (BA 47)(R)	34	24	-7	21	5.5×10^{-3}
Inferior frontal gyrus (BA 47)(L)	-32	25	-2	20	5.8×10^{-3}
Insula/Clastrum (L)	-30	17	6	20	5.8×10^{-3}
Medial wall					
Medial frontal gyrus (BA 9)(R)	4	45	15	16	5.6×10^{-3}
Temporal lobe					
Superior temporal gyrus (BA 39)(R)	40	-58	28	18	5.6×10^{-3}
Cerebellum					
Cerebellum posterior, declive (R)	34	-68	-19	17	5.6×10^{-3}
Controls>ADHD					
Frontal lobe					
Inferior frontal gyrus (BA 47)(L)	-44	19	2	78	6.5×10^{-3}
Precentral gyrus (BA 44)(R)	44	15	6	67	6.6×10^{-3}
Precentral gyrus (BA 6)(L)	-34	-1	38	22	6.0×10^{-3}
Medial wall					
Cingulate gyrus (BA 24)(R)	2	9	34	36	6.0×10^{-3}
Parietal lobe					
Superior parietal lobe (BA 7)(L)	-42	-61	55	16	1.0×10^{-3}
Basal ganglia					
Caudate (body) (R)	14	0	23	40	5.9×10^{-3}
ADHD>Controls					
Frontal lobe					
Medial frontal gyrus (BA 10)(L)	-14	51	-7	16	1.0×10^{-3}
Parietal lobe					
Paracentral lobule (BA 5)(R)	12	-34	48	132	7.2×10^{-3}

BA = Brodmann area, L = left, R = right, cluster threshold = 16 voxels.

*False Discovery Rate (FDR) corrected p values.

areas of the left occipital cortex (BA 18, BA 19) and sub-cortical areas of the right temporal lobe (BA 37). Subjects with ADHD showed significantly higher probability of activation than controls in areas of left frontal lobe in insula (BA 13) and middle frontal gyrus (BA 9, BA 10) and right precentral gyrus (BA 9), along with bilateral thalamus and right lentiform nucleus.

Children and adolescents only

While most studies included in our meta-analyses focused on ADHD in children and adolescents, five studies examine ADHD in adult populations instead (Bush et al., 1999; Ernst et al., 2003; Schweitzer et al., 2000, 2004; Valera, Faraone, Biederman, Poldrack, & Seidman, 2005). These studies were included in our analyses in order to maximize our ability to detect ADHD-related differences across studies. However, one possible risk of this approach is that the neural correlates of ADHD in adults may differ to some degree from the findings in children and adolescents, resulting in the introduction of unintended heterogeneity that may decrease our ability to detect ADHD-related differences. In order to address this concern, all meta-analyses were repeated with the five adult studies excluded (all of which were non-inhibition studies). Removal of the heterogeneity introduced by the adult studies did not result in detection of additional regions reflecting group differences.

Overall, the results of our meta-analyses excluding adult studies were highly similar to those obtained when the adult studies were included, though markedly less robust. Such reductions in effect size were expected due to a smaller sample size (see Table 4 and Figure 2). While most group differences remained detectable at $p < .05$ corrected (see Table 4), a more lenient threshold of $p < .005$ uncorrected was employed in Figure 2 to demonstrate the high degree of similarity to overall (adult + child/adolescent) group differences. While these findings do not exclude the possibility that the neural correlates of ADHD may differ in children and adolescents versus adults, they do suggest a reasonable degree of overlap.

Discussion

In line with models implicating frontal lobe dysfunction in ADHD, our meta-analyses provided objective, unbiased evidence of a consistent pattern of frontal hypoactivity in patients with ADHD compared to controls across 16 peer-reviewed neuroimaging studies. The frontal hypoactivity noted in patients with ADHD is widely distributed, affecting anterior cingulate, dorsolateral prefrontal, inferior prefrontal, and orbitofrontal cortices, as well as related regions, such as portions of the basal ganglia and parietal cortices.

While our findings are primarily centered in frontal regions, they should not be over-interpreted as suggesting that frontal dysfunction alone underlies ADHD. All of the tasks from studies included in our meta-analysis were designed to isolate executive processes, which are primarily supported by fronto-striatal and fronto-parietal neural networks. Despite differences in the specific executive process being examined across studies, our findings confirm the effectiveness of such an approach in detecting group differences in a set of frontal regions common to the processes examined. Of course, our findings may be an underestimate for some individual processes that may uniquely activate a broader range of regions. Evidence for this comes from our findings of ADHD-related caudate hypofunction in the response-inhibition-only meta-analysis, but not in the larger combined meta-analysis. To fully establish the primacy of frontal dysfunction in ADHD, future studies will need to provide a more comprehensive examination of executive function, as well as other cognitive domains, using tasks known to produce consistent patterns of activity in other regions considered putative sources of dysfunction (e.g., cerebellum, ventral striatum, parietal cortices). In the absence of such a literature, we can only conclude that robust evidence of frontal hypofunction exists in ADHD.

Given the prominence of response-inhibition tasks in the ADHD literature, the present work provided a separate analysis focusing on this subset of studies alone, once again finding evidence of frontal hypofunction, albeit less widespread. More specifically, a meta-analysis carried out across ten contrasts isolating response inhibition revealed relatively small areas of frontal hypofunction within inferior frontal, medial wall regions (including anterior cingulate cortex) and the precentral gyrus. The limited findings for the meta-analysis focusing on inhibition alone may reflect the smaller number of studies included, though ten contrasts should be enough to obtain relatively robust findings based on prior work. Alternatively, the suggestion that response inhibition relies on a fairly focal network within the brain (Aron et al., 2005) may be responsible for the sparse results found here. In order to further examine this possibility, we carried out a meta-analysis of the non-inhibition studies alone, finding a highly similar pattern to the combined meta-analysis, suggesting that the findings for non-inhibition studies tend to be more robust than those focusing on response inhibition.

With respect to further examination of frontal dysfunction in ADHD, we believe that a recent distinction between types of executive function may be usefully explored in future efforts. Zelazo and colleagues differentiate between 'hot' (i.e., affective) and 'cool' (i.e., non-affective) subtypes of executive function, involving orbitofrontal and dorsolateral prefrontal areas, respectively. As reviewed elsewhere

Table 4 Group differences: child/adolescent participants only. Regions of significant elevated probability of activation

	x	y	z	Cluster size (voxels)	p*
Controls>ADHD					
Frontal lobe					
Middle frontal gyrus (BA 9)(R)	50	18	29	34	5.0×10^{-3}
Inferior frontal gyrus (BA 47)(L)	-24	28	-9	31	5.1×10^{-3}
Superior frontal gyrus (BA 6)(R)	20	-3	71	28	5.3×10^{-3}
Inferior frontal gyrus (BA 9)(R)	52	4	30	27	5.3×10^{-3}
Precentral gyrus (BA 4)(L)	-34	-27	56	26	5.3×10^{-3}
Middle frontal gyrus (BA 6)(L)	-20	-2	56	24	5.3×10^{-3}
Middle frontal gyrus (BA 10)(L)	-42	41	23	22	5.4×10^{-3}
Insula (BA 13)(L)	-34	25	9	21	5.5×10^{-3}
Superior frontal gyrus (BA 6)(L)	-4	12	57	21	5.4×10^{-3}
Superior frontal gyrus (BA 8)(L)	-2	30	44	21	5.3×10^{-3}
Medial wall					
Cingulate (BA 31)	0	-24	39	29	5.3×10^{-3}
Cingulate gyrus (BA 24)(R)	12	-4	49	24	5.4×10^{-3}
Medial frontal gyrus (BA 6)(L)	-6	0	49	21	5.5×10^{-3}
Parietal lobe					
Precuneus (BA 7)(L)	-16	-71	50	33	5.1×10^{-3}
Postcentral gyrus (BA 3)(R)	38	-28	52	31	5.1×10^{-3}
Superior parietal lobule (BA 5)(L)	-18	-39	60	28	5.2×10^{-3}
Precuneus (BA 7)(L)	-8	-63	39	26	5.4×10^{-3}
Postcentral gyrus (BA 3)(R)	24	-35	52	25	5.4×10^{-3}
Superior parietal lobule (BA7)(R)	26	-65	48	25	5.3×10^{-3}
Basal ganglia					
Lentiform nucleus (R)	24	15	0	21	5.5×10^{-3}
Occipital lobe					
Middle occipital gyrus (BA 19)(L)	-28	-78	12	76	5.6×10^{-3}
Temporal lobe					
Superior temporal gyrus (BA 22)(L)	-50	-47	14	32	5.3×10^{-3}
ADHD>Controls					
Frontal lobe					
Inferior frontal gyrus (BA 9)(L)	-44	16	22	201	5.8×10^{-3}
Middle frontal gyrus (BA 10)(L)	-38	44	8	109	6.0×10^{-3}
Middle frontal gyrus (BA 9)(L)	-30	22	33	32	5.1×10^{-3}
Middle frontal gyrus (BA 46)(R)	38	40	3	31	5.1×10^{-3}
Precentral gyrus (BA 9)(R)	36	5	36	27	5.2×10^{-3}
Inferior frontal gyrus (BA 44)(R)	52	10	15	25	5.4×10^{-3}
Middle frontal gyrus (BA 6)(L)	-26	14	57	21	5.1×10^{-3}
Medial wall					
Anterior cingulate gyrus (BA 32)(R)	6	35	19	25	5.3×10^{-3}
Medial frontal gyrus (BA 8)(L)	-2	19	46	25	5.1×10^{-3}
Parietal lobe					
Postcentral gyrus (BA 2)(R)	40	-25	32	25	5.3×10^{-3}
Basal ganglia					
Caudate (R)	6	17	15	31	5.2×10^{-3}
Lentiform nucleus (R)	10	1	-1	16	5.6×10^{-3}
Temporal lobe					
Superior temporal gyrus (BA 38)(L)	-40	6	-15	18	5.5×10^{-3}

BA = Brodmann area, L = left, R = right, cluster threshold = 16 voxels.

*False Discovery Rate (FDR) corrected *p* values.

(Castellanos, Sonuga-Barke, Milham, & Tannock, 2006), despite the emphasis of the current ADHD literature on deficits in 'cool' executive function, a large-scale meta-analysis of behavioral studies involving executive function found that while statistically significant, effect sizes of these deficits were modest at best (Willcutt et al., 2005). Of note, group differences extending in the present meta-analysis extended into left orbitofrontal cortex, a putative 'hot' area, despite the tendency of most studies to use tasks designed to assess the 'cool' DLPFC and cingulate regions. These findings support the expansion of the scope of experimental paradigms to expressly

target regions associated with 'hot' executive function and affectively laden processing, such as the orbitofrontal cortices and related ventral striatal areas.

Although a consistent theme in the current ADHD literature, some caution should be taken in making inferences about the significance of 'frontal hypoactivity.' While typically thought to reflect a decrease in the intensity of activation in a particular region, it may also reflect decreases in the spatial extent of activations, more spatial dispersion of activations, decreases in functional connectivity, or more statistical noise (possibly due to factors such as more

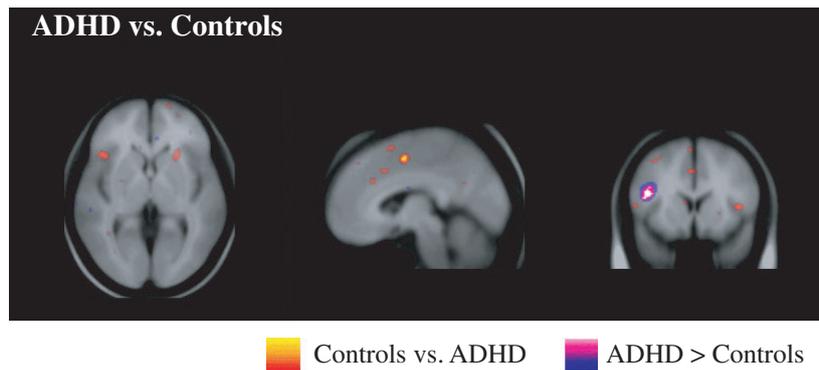


Figure 2 ALE meta-analyses for child and adolescent participants only. While similar in distribution to meta-analyses including both adults and children, results from the child-only analyses were less robust. For all images: $x = -5$, $y = 13$, $z = 1$ respectively, $p < .005$ uncorrected

variable responses in or greater motion in patients). Similarly, it is important to note that our analyses suggested that some regions show locally greater activations for patients with ADHD when compared to controls, suggesting that ADHD is not purely accounted for by hypofunction. These increases may reflect compensatory recruitment of accessory brain regions to accomplish a given cognitive task or alternatively an abnormally increased activation that interferes with typically recruited brain regions. Further work is merited to clarify the nature of both findings of decreased and increased activity associated with ADHD.

Despite our success in demonstrating consistencies in findings across studies, specific methodological limitations should be considered with respect to the current functional neuroimaging literature examining ADHD. First, only nine of the studies included in this meta-analysis reported direct comparisons between participants with ADHD and healthy controls and those that do provide such direct comparisons tend to use small sample sizes, thereby limiting their ability to detect subtle between-group differences. By creating a difference map between ALE estimates of participants with ADHD and controls we were able to include the seven studies that did not report direct comparisons and thus create a meta-analysis across all 16 of the studies in the literature that examined cognitive constructs reported results for individual participant groups and reported results in stereotactic coordinates. Second, multiple studies in the literature did not report their results in standard 3-D stereotactic coordinates, and only reported their findings in terms of anatomically determined regions of interest. Without the use of standardized 3-D coordinates, comparisons between these studies must rely on more subjective approaches and cannot be included in voxel-based, statistical meta-analyses such as the present study. Despite exclusion of these studies, our results are broadly consistent with those of qualitative reviews that included both studies with and without stereotactic coordinates. Finally, an-

other related concern is that even studies reporting stereotactic coordinates focused their results based on regions of interest rather than on whole brain analyses, potentially missing other putative sources of dysfunction, such as cerebellum and ventral striatum.

Variability in statistical approaches employed in the literature is another potential methodological concern, in particular with respect to corrections for multiple comparisons and threshold selection. These differences impact rates for false positives and false negatives. ALE addresses this issue by weighting the findings of each peer-reviewed study equally and relying upon patterns of consistency across studies to overcome this concern. Two notable risks of this approach are that studies with less stringent thresholds can introduce a larger number of foci, and that higher- and lower-powered studies have equal weighting. In our meta-analyses, such confounds are not more likely to impact one group than the other, as we only included studies that provide results for patients with ADHD and controls. In a study with a lenient threshold, both groups will benefit and have a greater number of foci, thus nullifying the effect on group differences. Furthermore, as a test of the possibility that differences in number of foci alone may be driving our group differences, we matched the two groups for number of foci by randomly selecting and dropping foci from the control group and reran the meta-analyses (Laird et al., 2005a). No marked differences in the pattern of results were observed.

Finally, the presence of substantial heterogeneity with regard to study samples is another notable limitation of the current literature. In particular, differences in the age ranges examined across studies may be a source of concern. Both age-related differences in the expression of ADHD symptoms and potential age-related differences in patterns of functional activity can complicate the integration of findings across studies. At present, there are not yet a sufficient number of studies of ADHD in either adult or pediatric populations to distinguish age-

related or developmental effects. Other notable sources of heterogeneity include medication history, ADHD subtypes, medication status during imaging, and age of onset. Despite these multiple sources of heterogeneity, our meta-analyses suggests that commonalities across patients with ADHD in the range of tasks examined to date are not obliterated by the undoubted heterogeneity encompassed within this diagnostic category.

In conclusion, our findings draw attention to the presence of consistent differences in the neural substrates of cognitive function between participants with and without a diagnosis of ADHD across studies. This has significant implications for future studies of the neuropathophysiology of ADHD, highlighting consistently identified regions across studies. The results of this meta-analysis do not support simpler models which posit that ADHD is strictly a disorder resulting from deficits of activity in a few isolated brain regions. Thus, a continued examination of the cognitive substrates of ADHD is needed.

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