Meta-analysis of Functional Magnetic Resonance Imaging Studies of Inhibition and Attention in Attention-deficit/Hyperactivity Disorder

Exploring Task-Specific, Stimulant Medication, and Age Effects

Heledd Hart, PhD; Joaquim Radua, MD; Tomohiro Nakao, MD, PhD; David Mataix-Cols, PhD; Katya Rubia, PhD

Context: Functional magnetic resonance imaging studies in attention-deficit/hyperactivity disorder (ADHD) revealed fronto-striato-parietal dysfunctions during tasks of inhibition and attention. However, it is unclear whether task-dissociated dysfunctions exist and to what extent they may be influenced by age and by long-term stimulant medication use.

Objective: To conduct a meta-analysis of functional magnetic resonance imaging studies in ADHD during inhibition and attention tasks, exploring age and long-term stimulant medication use effects.

Data Sources: PubMed, ScienceDirect, Web of Knowledge, Google Scholar, and Scopus databases were searched up to May 2012 for meta-analyses. Meta-regression methods explored age and long-term stimulant medication use effects.

Study Selection: Twenty-one data sets were included for inhibition (287 patients with ADHD and 320 control subjects), and 13 data sets were included for attention (171 patients with ADHD and 178 control subjects).

Data Extraction: Peak coordinates of clusters of significant group differences, as well as demographic, clinical, and methodological variables, were extracted for each study or were obtained from the authors.

Data Synthesis: Patients with ADHD relative to controls showed reduced activation for inhibition in the right inferior frontal cortex, supplementary motor area, and anterior cingulate cortex, as well as striato-thalamic areas, and showed reduced activation for attention in the right dorsolateral prefrontal cortex, posterior basal ganglia, and thalamic and parietal regions. Furthermore, the meta-regression analysis for the attention domain showed that long-term stimulant medication use was associated with more similar right caudate activation relative to controls. Age effects could be analyzed only for the inhibition meta-analysis, showing that the supplementary motor area and basal ganglia were underactivated solely in children with ADHD relative to controls, while the inferior frontal cortex and thalamus were underactivated solely in adults with ADHD relative to controls.

Conclusions: Patients with ADHD have consistent functional abnormalities in 2 distinct domain-dissociated right hemispheric fronto-basal ganglia networks, including the inferior frontal cortex, supplementary motor area, and anterior cingulate cortex for inhibition and dorsolateral prefrontal cortex, parietal, and cerebellar areas for attention. Furthermore, preliminary evidence suggests that long-term stimulant medication use may be associated with more normal activation in right caudate during the attention domain.

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ATTENTION-DEFICIT/HYPERactivity disorder (ADHD) is one of the most debilitating childhood disorders, defined by age-inappropriate impulsiveness, inattention, and hyperactivity,[1] persisting into adulthood in about 65% of cases.[2] Patients with ADHD have consistent deficits in motor response and interference inhibition, as well as in attention, in particular selective, sustained, and flexible attention.[3,4]

Patients with ADHD show fronto-striato-thalamo-parietal brain dysfunctions during inhibition tasks, most prominently in right inferior frontal cortex (IFC), supplementary motor area (SMA), caudate, and thalamus during go/no-go[5-9] and stop[10-16] tasks and in the bilateral IFC, anterior cingulate cortex (ACC), basal ganglia, and parieto-temporal regions during interference inhibition tasks.[16-22] More recently, functional magnetic resonance imaging (FMRI) studies demonstrated reduced activation in the bilateral dorsolateral prefrontal cortex (DLPFC) and IFC, basal ganglia, and parieto-temporal

Author Affiliations are listed at the end of this article.

regions during attention allocation[18,19,23,24] and during sustained,[25] selective,[5,26] and flexible attention.[9,10,27-29]

However, it is unclear whether patients with ADHD have different or overlapping fronto-basal ganglia-parietal dysfunctions during these 2 cognitive domains, mediated by parallel fronto-basal ganglia-thalamo-parietal networks.[30] Furthermore, there have been conflicting reports of increased activation in patients with ADHD relative to control subjects during inhibition tasks in mesial frontal, parieto-temporal, and cingulate regions[6,7,12,17,31-33] and during attention tasks in posterior parieto-temporal, cerebellar, and occipital brain regions.[25,29,34-36] Variability between studies may be due to differences in age and in long-term stimulant medication use, given that both were associated with more normal basal ganglia volumes in a structural meta-analysis.[37]

A previous meta-analysis[38] using activation likelihood estimation, conducted in 16 FMRI studies in 2006, found consistent deficits in patients with ADHD relative to controls across a range of inhibition and attention tasks in bilateral DLPFC, IFC, ACC, parietal, and striato-thalamic regions, as well as overactivation in the left thalamus, insula, and medial frontal lobe. However, the analysis included region-of-interest FMRI analyses,[38] which provide a constrained characterization of functional anatomy.[39] Also, likely due to limited methods and study availability at the time, meta-analyses were performed across group maps, rather than on coordinates of differences from individual studies, and included a wide range of FMRI paradigms of inhibition, timing, and attention tasks, as well as other imaging modalities. Given that FMRI activation is critically paradigm dependent, it is paramount to meta-analyze FMRI studies that focus on the same underlying cognitive constructs. Finally, activation likelihood estimation meta-analysis does not allow for meta-regression analyses, which can assess potential confounds such as age and long-term stimulant medication use.

In this meta-analysis, we aimed to overcome these limitations by including only whole-brain analysis FMRI studies of inhibition and attention paradigms, analyzing both domains independently. In addition, we tested for effects of age and long-term stimulant medication history in meta-regression analyses.

For the inhibition domain, go/no-go and stop tasks were included for motor response inhibition, and Simon, Eriksen flanker, and Stroop tasks were included for interference inhibition. Both inhibitory domains involve the inhibition of a prepotent motor response to an infrequent stimulus among a string of high-frequent stimuli and measure conflict detection. A meta-analysis[40] of these tasks in healthy adults has shown that motor and interference inhibition is mediated by overlapping fronto-striato-thalamo-parietal networks, including predominantly the right hemispheric IFC, SMA, ACC, caudate, thalamus, and inferior parietal regions. Because there were large enough numbers of FMRI studies on motor and interference inhibition tasks, we further subdivided the 2 inhibitory domains to increase homogeneity. Go/no-go and stop tasks are considered to tap into the same cognitive construct of motor response inhibition,[41-47] the difference being the timing of the stop signal, which in the stop task occurs shortly after the go signal, making it more difficult to inhibit.[47,48] This is reinforced by the cognitive neuroimaging literature, which shows that both tasks are mediated by overlapping networks of right IFC, SMA, ACC, caudate, and parietal areas.[40,44,45,47] Interference inhibition tasks, rather than measuring motor response inhibition directly, measure the ability to inhibit conflicting information that interferes with the primary intended action and may only lead to an erroneous motor response, if not ignored.[40,42] These tasks have a higher load on cognitive inhibition (ie, conflict detection and inhibition of distraction), as opposed to motor inhibition tasks that load higher on motor response suppression.[42,44] Neurofunctionally, this subdivision is reinforced by differences in the underlying neural networks, with interference inhibition tasks showing stronger activation of the left ACC and left IFC, crucial for conflict inhibition, while motor response inhibition tasks in turn activate more strongly the SMA and right IFC.[40,44]

For the attention domain, the FMRI literature is more heterogeneous, and studies have used a larger variety of tasks. Therefore, we included a range of tasks measuring visuospatial selective attention (including oddball and divided attention tasks), sustained attention (continuous performance task), and flexible attention (ie, the ability to rotate representations of visual objects in attention in mental rotation tasks). Visuospatial attention tasks typically activate a network of lateral IFC and DLPFC, basal ganglia, thalamic, parieto-temporal, and cerebellar brain regions.[49,50] Further subdivision of these attention tasks was not possible due to the limited number of studies.

We hypothesized that patients with ADHD would show consistent and dissociated domain-specific fronto-basal ganglia-parietal brain dysfunctions in IFC, ACC, SMA, and caudate networks for inhibition and in DLPFC and basal ganglia-parieto-cerebellar networks for attention. Furthermore, 2 recent meta-analyses[37,51] of structural imaging studies showed that long-term stimulant medication use is associated with more normal basal ganglia structure. Given that basal ganglia function is also modulated by long-term medication use,[52] we expected that across both cognitive domains, basal ganglia function would be less severely impaired in patients with long-term medication use. Finally, given evidence from longitudinal and meta-analytical structural imaging studies[37,53] showing that basal ganglia deficits in ADHD appear to normalize with age, we expected younger patients with ADHD to have more severe basal ganglia dysfunctions than adults with ADHD.

METHODS

A comprehensive literature search of FMRI studies in ADHD using inhibition and attention tasks was conducted on PubMed, ScienceDirect, Web of Knowledge, Google Scholar, and Scopus search engines up to May 2012. The search keywords were *attention-deficit/hyperactivity disorder*, *ADHD* or *hyperkinetic*, plus *FMRI*, plus *inhibition*, *stop*, *Stroop*, *flanker*, *go/no-go*, *Simon*, *interference*, *attention*, *CPT* [continuous performance task], *selective attention*, *divided attention*, *target detection*, *mental rotation*, and *cognitive flexibility*. In addition, manual searches were conducted within review articles and reference sections of in-

dividual studies. Excluded were studies that (1) contained subject overlap within the same task with other studies, (2) did not include healthy controls, (3) used a region-of-interest approach, (4) included medicated patients with no washout period before FMRI, and (5) did not report coordinates for the relevant contrasts and did not or could not supply these when the authors were contacted. The corresponding authors were asked to provide additional details not included in the original publications. Meta-analysis of Observational Studies in Epidemiology guidelines for meta-analyses of observational studies were followed in the study.[54]

The following 2 main meta-analyses were performed: (1) one for inhibition tasks, further divided into motor response and interference inhibition, including stop and go/no-go (motor inhibition), Stroop, Simon, or Eriksen flanker tasks (interference inhibition), and (2) the other for attention tasks, including cued target detection and oddball (attention allocation), selective and divided attention (including alerting and orienting), continuous performance task (sustained attention), and mental rotation tasks (attentional flexibility). For all meta-analyses, peak coordinates of activation differences between patients with ADHD and controls were extracted from each data set for the following contrasts: stop or go/no-go (motor inhibition) and incongruent-congruent (Simon, Eriksen flanker, and Stroop tasks). For attention tasks, the following were used: cue plus target minus target only (cued target detection), oddball minus standard trials (oddball tasks), target minus nontarget trials (continuous performance task), rotation minus baseline (mental rotation), alerting-orienting minus baseline trials (alerting-orienting), and divided or selective attention minus baseline trials (divided or selective attention). Peaks that were not statistically significant at the whole-brain level were excluded.

Regional group differences in activation during inhibition and attention tasks were analyzed using a software program (effect size signed differential mapping; http://www.sdmproject.com/), a voxel-based meta-analytic approach that uses the reported peak coordinates to re-create maps of the effect size of group differences in blood oxygenation level–dependent response. For peak coordinates, the re-creation is based on first converting the peak *t* value to Hedges effect size and then applying a nonnormalized gaussian kernel to the voxels close to the peak. The signed differential mapping methods have been described in detail elsewhere,[55-58] and only the main points are summarized herein.

First, only data sets in which the same threshold was used throughout the whole brain were included. Second, activations and deactivations were re-created in the same map to correctly analyze those regions with higher between-study heterogeneity. If activations and deactivations were plotted in separate maps, noisy regions could falsely appear as activating and deactivating at the same time, which is logically impossible.[56] Third, studies were combined with a random-effects model as in standard meta-analyses, taking into account sample size, intrastudy variability, and between-study heterogeneity.[58]

These analyses were complemented with analyses of robustness. In case of significant heterogeneity within a brain region found to abnormally respond in patients, we used funnel plots to check whether findings might have been driven by few or small studies, as well as to detect gross abnormalities such as studies reporting opposite results.[56,57] Also, we conducted a jackknife sensitivity analysis consisting of iteratively repeating the same analysis, excluding one data set at a time to establish whether the results were replicable.[55]

Statistical significance was determined using standard permutation tests. Null distributions were created, from which *P* values could be directly obtained.

For inhibition, we conducted a meta-regression analysis with age, which could not be done for attention due to only 2 studies in adults. For both analyses, we conducted meta-regression analyses for the percentage of patients receiving long-term stimulant medication.

RESULTS

INCLUDED STUDIES AND CHARACTERISTICS

The search retrieved a total of 65 data sets (28 for motor inhibition, 18 for interference inhibition, 18 for attention, and 1 requiring both inhibition and attention). Excluded were 14 data sets due to the use of anatomical regions of interest or regions of interest for analysis of variance based on whole-brain group activation,[7,17,59-70] 6 studies[9-11,16,19,71] due to patient overlap, 4 studies[72-75] due to lack of control groups, 2 studies[76,77] that could not provide coordinates for the relevant contrasts, 2 studies[78,79] that used emotional Stroop tasks, 1 study[34] that required both inhibitory and attentional processes, and 1 study[33] that included 50% of patients with undiagnosed ADHD (eFigure; http://www.jamapsych.com).

Finally, 21 high-quality data sets were included in the inhibition meta-analysis, including 7 adult samples[15,18,21,22,31,80,81] and 14 pediatric samples.* Thirteen high-quality data sets were included in the attention meta-analysis (2 adult samples[18,35] and 11 pediatric samples†). Combined, the inhibition studies included 287 patients with ADHD and 320 healthy controls (**Table 1**), and the attention studies included 171 patients with ADHD and 178 healthy controls (**Table 2**). All data sets that included medicated patients used a washout period of at least 18 hours before FMRI.

META-ANALYSIS FOR INHIBITION

For all inhibition tasks together, patients having ADHD compared with controls showed significantly decreased activation in the right IFC extending into insula, a cluster comprising the SMA and the cognitive division of the ACC (Brodmann area 32/24),[89] and the left caudate extending into the putamen and insula and right mid-thalamus (**Table 3**, **Figure 1**A, and **Figure 2**A). No significantly increased activations were observed for patients with ADHD relative to controls.

During motor response inhibition only, patients with ADHD (n = 187) relative to controls (n = 206) showed significantly decreased activation in the right IFC and insula, right SMA and ACC, right thalamus, left caudate, and right occipital lobe (Table 3 and Figure 2B).

For interference inhibition only, patients with ADHD (n = 100) relative to controls (n = 114) showed

References 5, 6, 9, 12-14, 16, 20, 32, 82-86.
†*References 5, 19, 23-26, 28, 29, 52, 87, 88.*

Table 1. Inhibition Tasks

Source	Task	Patients With ADHD: No. (% Male)	Patients With ADHD: Mean Age, y	Patients With ADHD: % Medicated (Time Stopped, h)	Patients With ADHD: % Comorbidities (Type)	Healthy Controls: No. (% Male)	Healthy Controls: Mean Age, y	Brain Regions Activated: Controls > ADHD	Brain Regions Activated: ADHD > Controls
Motor Inhibition									
Booth et al,[5] 2005	GNG	12 (66.7)	11	100 (48)	0	12 (58.3)	11.7	R SFG, IFC, ACC, B MFG; B preCG, amygdala, fusiform, thalamus B caudate; L GP cuneus	/
Dibbets et al,[80] 2009	GNG	16 (100)	28.9	87.5 (24)	0	13 (100)	28.1	/	/
Durston et al,[6] 2003	GNG	7 (85.7)	8.55	100 (24)	?	7 (85.7)	8.68	L caudate	R SFG, inf PL, STG, MFB, BL occipital, precuneus, PCC
Durston et al,[82] 2006	GNG	11 (100)	13.97	54.5 (24)	27.27 (ODD)	11 (100)	15.27	/	/
Karch et al,[81] 2010	GNG	8 (87.5)	38.3	0	0	8 (87.5)	37.8	L preCG, SFG; R IPL	L postCG, MFG
Kooistra et al,[31] 2010	GNG	11 (100)	21.5	0	0	11 (100)	22.3	/	R ACC, SMG
Smith et al,[9] 2006	GNG	17 (100)	12.8	0	29.41 (CD)	18 (100)	14.1	L MFG	/
Spinelli et al,[85] 2011	GNG	13 (69.2)	10.6	15.4 (48)	23.07 (ODD, simple phobia)	17 (47)	10.5	/	R preCG, BL MFG
Suskauer et al,[86] 2008	GNG	25 (60)	10.8	75 (48)	56 (ODD, simple phobia)	25 (60)	10.8	/	/
Tamm et al,[32] 2004	GNG	10 (100)	16.0	50 (18)	0	12 (100)	15.58	R ACC, SMA, SFG, MFG	L mid/inf/sup TL
Cubillo et al,[15] 2010	Stop	11 (100)	29	0	77 (Anxiety, mood, CD, SA)	14 (100)	28	R IFC, insula, thalamus, putamen, caudate	/
Passarotti et al,[14] 2010	Stop	11 (54.55)	13.09	53 (1 wk)	0	15 (46.66)	14.13	R MFG, SFG	BL caudate, L cerebellar vermis
Rubia et al,[13] 2005	Stop	16 (100)	13	0	31.25 (CD)	21 (100)	14.0	R IFC, OFC, preCG, STL	/
Rubia et al,[12] 1999	Stop	7 (100)	15.71	0	42.86 (CD)	9 (100)	15.01	R IFC, MFG, L caudate	/
Rubia et al,[84] 2011	Stop	12 (100)	13	0	8.33 (ODD, CD)	13 (100)	13	B IFC, insula, ACC, preSMA; thalamus; R MTL, occipital, IPL, precuneus, PCc, cerebellum	/
Interference Inhibition									
Cubillo et al,[18] 2011	Simon	11 (100)	29	0	77 (Anxiety, mood, CD, SA)	15 (100)	28	L OFC, IFC, MFC, AAC, caudate, preCG	/
Rubia et al,[16] 2011	Simon	12 (100)	13	0	8.33 (ODD/CD)	13 (100)	13	R IFC, SMA, ACC, sup/in PL, PCC, L MFC, BG, thalamus, STL/MTL, occipital	/
Rubia et al,[20] 2011	Simon	18 (100)	14.25	0	5.55 (CD)	20 (100)	14.42	R SMA, ACC, supp/IPL	/
Banich et al,[21] 2009	Stroop	23 (60.8)	20.0	87.0 (24)	0	23 (56.5)	19.0	L IPL	R MFG, cuneus
Burgess et al,[22] 2010	Stroop	20 (60)	20.1	65 (24)	0	23 (56.5)	19.0	/	R SFG
Peterson et al,[83] 2009	Stroop	16 (81.2)	13.1	0	32.25 (Depression, ODD, specific phobias, SAD, GAD)	20 (60)	13.4	L ACC, insula R, precuneus, thalamus, caudate	R SFG, hippocampus, L ACC

Abbreviations: ACC, anterior cingulate cortex; ADHD, attention-deficit/hyperactivity disorder; B, bilateral; CD, conduct disorder; GAD, general anxiety diorder; GNG, go/no-go; GP, globus pallidus; IFC, inferior frontal cortex; IPL, inferior parietal lobe; L, left; MFG, middle frontal gyrus; MTL, medial temporal lobe; ODD, oppositional defiant disorder; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; preCG, precentral gyrus; postCG, postcentral gyrus; question mark, not reported; R, right; SA, substance abuse; SAD, separation anxiety disorder; SFG, superior frontal gyrus (lobe); SMA, supplementary motor area; STL, superior temporal lobe; TL, temporal lobe; virgule (/), no group difference.

Table 2. Attention Tasks

		Patients With ADHD				Healthy Controls		Brain Regions Activated	
Source	Task	No. (% Male)	Mean Age, y	% Medicated (Time Stopped)	% Comorbidities (Type)	No. (% Male)	Mean Age, y	Controls > ADHD	ADHA > Controls
Cao et al,[23] 2008	Cued target detection	12 (100)	13.4	25 (2 wk)	58.3 (ODD, CD)	13 (100)	13.2	B MFG, L SFG, R precuneus, preCG, SMA, putamen, IPL	
Rubia et al,[24] 2007	Oddball	17 (100)	13	0	29.4 (CD)	18 (100)	14	B STL, PCC, L MTL, insula, IPL, R putamen, caudate, thalamus	
Tamm et al,[88] 2007	Oddball	14 (100)	15.64	35.71 (18 h)	0	12 (100)	15.6	B IPL, precuneus, thalamus	
Cubillo et al,[18] 2011	Oddball	11 (100)	29	0	77 (Anxiety, mood, CD, SA)	15 (100)	28	L IFC, MFC, OFC, caudate	
Rubia et al,[19] 2009	Oddball	20 (100)	13.2	0	0	20 (100)	14.0	L IFC, MFC, R dMFC	
Cubillo et al,[35] 2012	CPT	11 (100)	29	0	77 (Anxiety, mood, CD, SA)	15 (100)	28	L IFC, insula, preCG, putamen, GP, postCG, PCC, precuneus, parhippocampal	B IPL/sup PL, cuneus, precuneus, PCC, cerebellum, occipital, L inf TL
Rubia et al,[25] 2009	CPT	18 (100)	13.3	0	0	16 (100)	13.10	B IFC/MFG	B cerebellum, occipital, hippocampus, thalamus, TL, L PCC, precuneus
Rubia et al,[87] 2009	CPT	13 (100)	12.5	0	7.69 (CD/ODD)	13 (100)	13.16	R IFC, vmOFC, B insula, thalamus, B IPL, STL, hippocampus, L putamen, caudate, parahippocampus cerebellum	
Konrad et al,[52] 2007	Alerting, orienting	9 (100)	11.1	0	44.4 (ODD, anxiety)	11 (100)	11.2		
Booth et al,[5] 2005	Selective attention	12 (66.7)	11	100 (48h)	0	12 (58.3)	11.7	MTL, sup PL, L fusiform, R cuneus	
Shafritz et al,[26] 2004	Selective and divided attention	15 (73.3)	15.1	53.3 (?)	? (CD, ODD)	14 (50)	16.6	L GP, putamen, B MTG	
Silk et al,[29] 2005	Mental rotation task	7 (100)	14.38	0	?	7 (100)	14.56	B IFC, L lateral SFG, caudate, precuneus, R IPL/sup PL, cuneus	L ventromedial SFG, STG, MTG, R PCC
Vance et al,[28] 2007	Mental rotation task	12 (100)	11.1	0	0	12 (100)	10.2	R caudate, precuneus, cuneus, IPL	

Abbreviations: ACC, anterior cingulate cortex; ADHD, attention-deficit/hyperactivity disorder; B, bilateral; CD, conduct disorder; dMFG, dorsomedial frontal gyrus; GP, globus pallidus; IFC, inferior frontal cortex; IPL, inferior parietal lobe; L, left; MFG, middle frontal gyrus; MTG, middle temproal gyrus; ODD, oppositional defiant disorder; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; preCG, precentral gyrus; postCG, postcentral gyrus; question mark, data not reported and therefore unknown; R, right; SFG, superior frontal gyrus (lobe); SMA, supplementary motor area; STG, superior temporal gyrus; TL, temporal lobe.

significantly decreased activation in the left cognitive division of ACC, right IFC and insula, right caudate head, and left posterior insula and parietal lobe (Table 3 and Figure 2C). However, findings should be considered with caution given the small number of studies included in this meta-analysis.

META-ANALYSIS FOR ATTENTION

For attention tasks, patients with ADHD relative to controls showed decreased activation in the right DLPFC, left putamen and globus pallidus, right posterior thalamus (pulvinar) and caudate tail extending into the posterior insula, and right inferior parietal lobe, precuneus, and superior temporal lobe. Relative to controls, patients with ADHD showed significantly increased activation in the right cerebellum and left cuneus (Table 3 and Figure 1B).

RELIABILITY ANALYSES

A whole-brain jackknife sensitivity analysis for all inhibition tasks together showed that the findings in the IFC and SMA or ACC were highly replicable, preserved throughout all 21 combinations of data sets. The results in the left basal ganglia remained significant in all but 1

Table 3. Meta-analyses Results for Functional Magnetic Resonance Imaging Studies of Inhibition Tasks and Attention Tasks

Contrast	Talairach x, y, z Coordinates	Signed Differential Mapping *z* Score	*P* Value	No. of Voxels	Breakdown (No. of Voxels)
All Inhibition Tasks Together					
Healthy controls > patients with ADHD					
Left and right SMA/ACC	−2, 6, 48	−2.568	<.001	726	BA 6 (403), BA 6 (195), BA 6/24/32 (128)
Right IFC/anterior insula	40, 16, 4	−1.869	<.001	225	Right BA 47/45 (151), right insula (33), right BA 44 (20), right BA 45 (17)
Left caudate head/putamen/anterior insula	−24, −4, 16	−1.485	<.001	82	Left caudate head/insula (22), left caudate head (26), left putamen (32)
Right thalamus	6, −18, 4	−1.381	.001	89	. . .
Patients with ADHD > healthy controls					
No significant effects	. . .	. . .	. . .	. . .	. . .
Motor Inhibition					
Healthy controls > patients with ADHD					
Right SMA/ACC	4, 10, 48	−2.580	<.001	644	BA 6 (447), BA 6 (111), BA 32 (85)
Right IFC/insula	36, 18, 8	−1.826	<.001	111	Right BA 45/47/insula (85), right BA 44 (10)
Right thalamus	4, −16, 4	−1.728	<.001	123	. . .
Left caudate head	−16, −8, 22	−1.461	.003	12	. . .
Right fusiform gyrus	26, −58, −8	−1.557	.002	26	Right BA 19
Interference Inhibition					
Healthy controls > patients with ADHD					
Left ACC	−2, 2, 40	−1.141	<.001	75	Left BA 24/32 (65), left BA 32 (10)
Right IFC/insula	46, 14, −4	−1.127	.001	108	Right BA 47/insula (49), right BA 47 (30), right BA 45 (10)
Right caudate head	16, −14, 22	−1.022	.002	11	. . .
Left posterior insula/parietal lobe	−36, −22, 20	−1.085	.002	39	Left BA 13/40
All Attention Tasks Together					
Healthy controls > patients with ADHD					
Right middle frontal (DLPFC)	26, 28, 44	−1.429	.002	46	Right BA 8 (46)
Left putamen/pallidus	−22, 0, −2	−2.091	<.001	658	Left putamen (414), left pallidum (188), left caudate (19)
Right thalamus (pulvinar)/caudate tail/posterior insula	20, −26, 16	−1.523	.001	101	Right thalamus/pulvinar (40), right posterior insula (36), right caudate (19)
Right inferior parietal	26, −48, 44	−1.690	<.001	74	Right BA 40 (47), right BA 7 (22)
Right precuneus	4, −54, 38	−1.367	.003	30	Right BA 7
Right superior temporal	58, −10, 12	−1.338	.003	19	Right BA 42 (10)
Patients with ADHD > healthy controls					
Right cerebellum	12, −72, −14	1.436	<.001	372	Right cerebellum (338), right BA 18 (34)
Left cuneus	−12, −76, 16	1.256	<.001	125	Left BA 18 (81), left BA 17 (27)
Effect of Stimulant Medication History					
Unmedicated patients < long-term medicated patients and healthy controls					
Right caudate tail	20, −26, 20	1.646	<.001	69	. . .
Long-term medicated patients < healthy controls < unmedicated patients					
Left cerebellum	−22, −54, −16	−2.176	<.001	254	Left cerebellum (235), left BA 19 (17)

Abbreviations: ACC, anterior cingulate cortex; ADHD, attention-deficit/hyperactivity disorder; BA, Brodmann area; DLPFC, dorsolateral prefrontal cortex; IFC, inferior frontal cortex; SMA, supplementary motor area; >, increased activation; <, decreased activation.

combination of data sets and in the right thalamus in all but 3 combinations of data sets (eTable 1). For motor response inhibition, the findings in the SMA were preserved throughout all 15 combinations of data sets. The results in the IFC remained significant in all but 1 combination of data sets, in the thalamus and fusiform gyrus in all but 2 combinations of data sets, and in the caudate in all but 2 combinations of data sets (eTable 2). For interference inhibition, the results in the ACC, posterior parietal lobe and insula, IFC, and caudate were preserved in all but 1 of 6 combinations of data sets (eTable 3).

The whole-brain jackknife sensitivity analysis for attention showed that the underactivation results in the left basal ganglia and right parietal and precuneus, as well as the overactivation findings in the right cerebellum and cuneus, were preserved throughout all of 13 combinations of data sets. The underactivation in the right thalamus and caudate was significant in all but 1 combination of data sets, and the underactivation in the right DLPFC was significant in all but 2 combinations of data sets (eTable 4).

EFFECT OF LONG-TERM STIMULANT MEDICATION USE

For inhibition, information on long-term stimulant medication use was available for all 21 data sets, with 97 patients (33.8%) receiving long-term stimulant medication at the time of the study (methylphenidate in 45, unidentified stimulants in 31, mixed amphetamine salts in 18, and D-amphetamine in 3). The meta-regression with medication was not significant.

For attention, information on long-term stimulant medication use was available for all 13 data sets, with 37 patients (21.6%) receiving stimulant medication at the time of the study (methylphenidate in 30, unidentified stimulants in 5, D-amphetamine in 1, and mixed amphetamine salts in 1) for periods ranging from 6 months to 3 years; patients were taken off medication between 18 hours and 2 weeks before the imaging. The meta-regression analysis with long-term stimulant medication use showed that the percentage of patients on long-term stimulant medication correlated significantly with increasing activation in the right caudate tail ($r = 0.233$, permutation-derived $P < .001$), so that medication-naive patients had significantly reduced activation compared with healthy controls ($z = 2.149$, $P < .001$) and with long-term medicated patients ($z = 1.646$, $P < .001$), who did not differ from each other (**Figure 3**). Given that long-term medication use may be confounded by age, the meta-regression analysis was repeated with age as a covariate. The primary regression finding remained.

Given that the right caudate was associated with long-term stimulant medication use in the attention analysis and was activated during the interference sub–meta-analysis, we conducted a meta-regression analysis with this cluster and long-term stimulant medication use. A trend was observed toward an association between long-term stimulant medication use and more normal right caudate activation, although this did not reach statistical significance, probably due to lack of power (it included only 6 studies).

EFFECT OF AGE

Because there were only 2 adult studies for the attention analysis, meta-regression analysis with age (age range, 8.5-38.3 years) was performed only for the inhibition analysis but showed no effects. However, when the data set was split categorically into an adult group (100 patients with ADHD and 107 controls) and a child group (187 patients with ADHD and 213 controls), only children with ADHD had decreased activation relative to controls in the left putamen and right caudate, as well as in the SMA and ACC, while only adult patients with ADHD had decreased activation relative to controls in the right IFC and right thalamus (**Figure 4**).

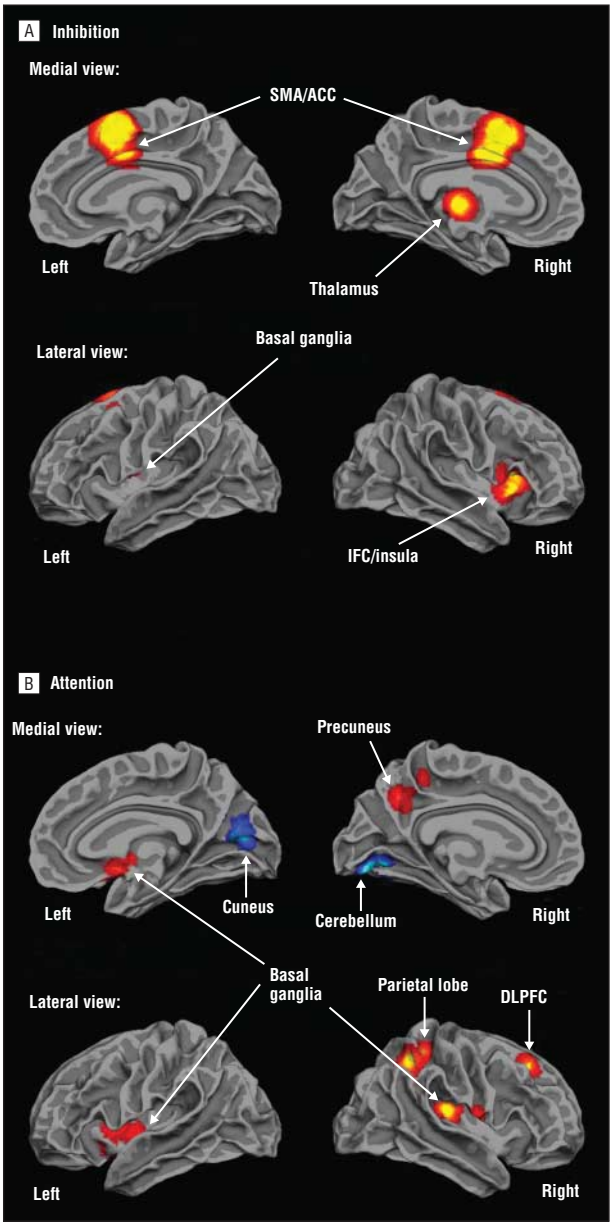

Figure 1. Inhibition tasks and attention tasks. A, All inhibition tasks together. Regions of decreased (red and orange) and increased (blue) activation in patients with attention-deficit/hyperactivity disorder compared with healthy controls. Decreased activation in patients with attention-deficit/hyperactivity disorder relative to healthy controls is shown in the right inferior prefrontal cortex (IFC) extending into the insula, in a cluster comprising the supplementary motor area (SMA) and the cognitive division of anterior cingulate cortex (ACC), in the left caudate extending into the putamen and insula, and in the right mid-thalamus. B, Attention tasks. Decreased activation in patients with attention-deficit/hyperactivity disorder is shown in the right dorsolateral prefrontal cortex (DLPFC), in the left putamen and globus pallidus, in the right posterior thalamus (pulvinar) and caudate tail extending into the posterior insula, in the right inferior parietal lobe, and in the precuneus and superior temporal lobe. Increased activation in patients with attention-deficit/hyperactivity disorder relative to healthy controls was seen in the left cuneus and in the right cerebellum.

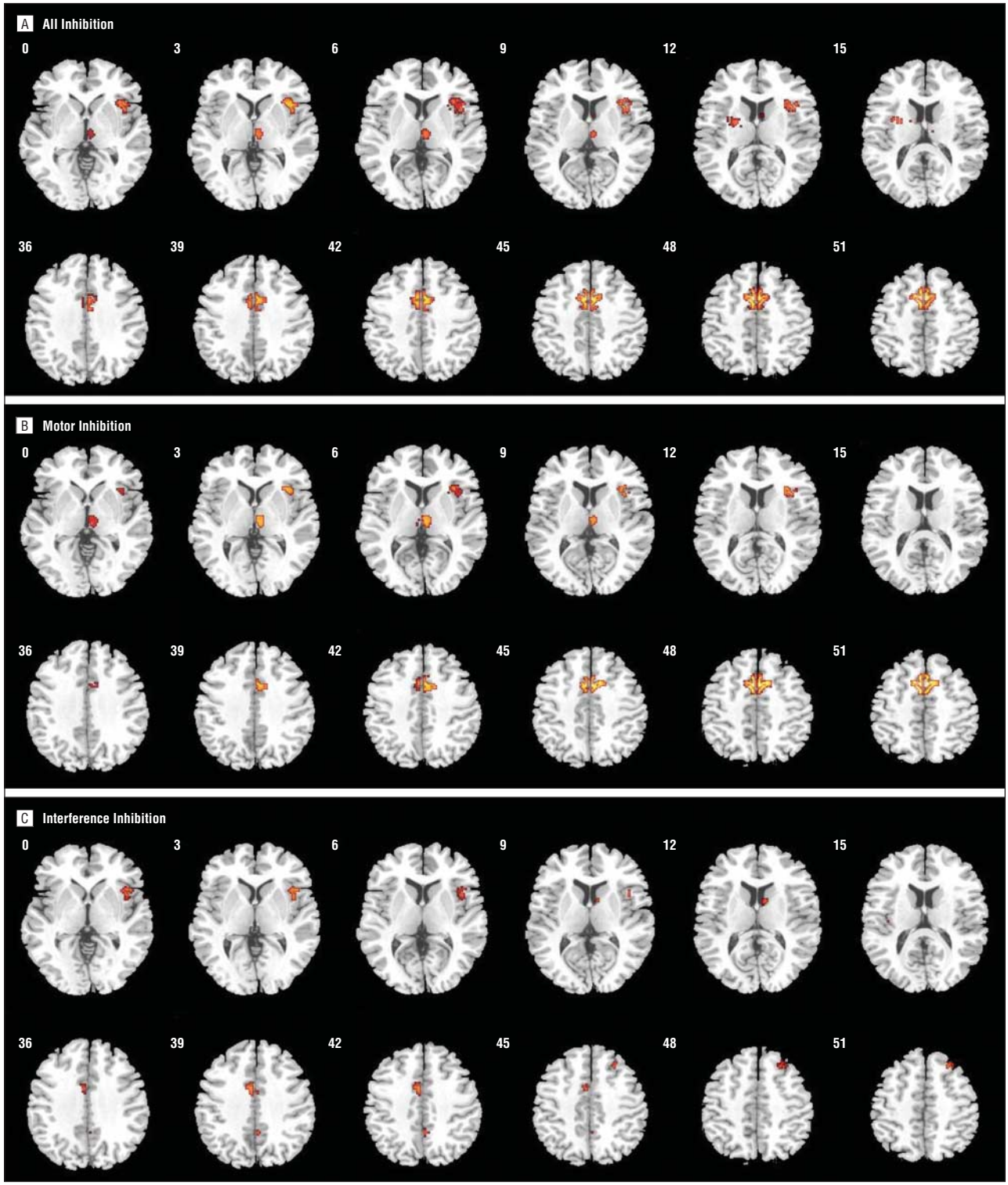

Figure 2. Inhibition tasks. A, All inhibition tasks together, with cross sections showing regions of decreased activation in patients with attention-deficit/hyperactivity disorder compared with healthy controls. Shown are the right inferior prefrontal cortex, insula, right thalamus, left caudate, left putamen, and left insula. B. Motor response inhibition only, showing the right inferior prefrontal cortex and insula, right supplementary motor area and anterior cingulate cortex, right thalamus, left caudate, and right fusiform gyrus. C, Interference inhibition only, showing the right inferior prefrontal cortex and insula, left anterior cingulate cortex, right caudate (head), and left posterior parietal lobe and posterior insula. The right side of the image corresponds to the right side of the brain. Distance from the anterior or posterior commissure is indicated in millimeters for the z coordinate.

COMMENT

This meta-analysis across FMRI studies of inhibition and attention functions shows task domain–specific, dissociated fronto-basal ganglia-thalamic dysfunctions in patients with ADHD. For inhibition tasks, patients with ADHD relative to controls showed consistent and replicable underactivation in typical regions of inhibitory con-

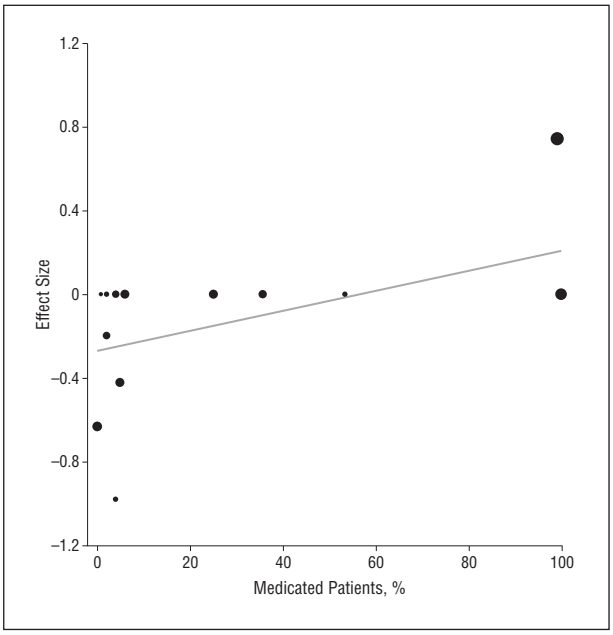

Figure 3. Results of the meta-regression analysis with stimulant medication effects for attention. Meta-regression analysis for attention shows that the percentage of patients receiving long-term psychostimulant treatment is associated with more normal right caudate activation relative to healthy controls. The regression line (meta-regression signed differential mapping slope) is presented as a straight line.

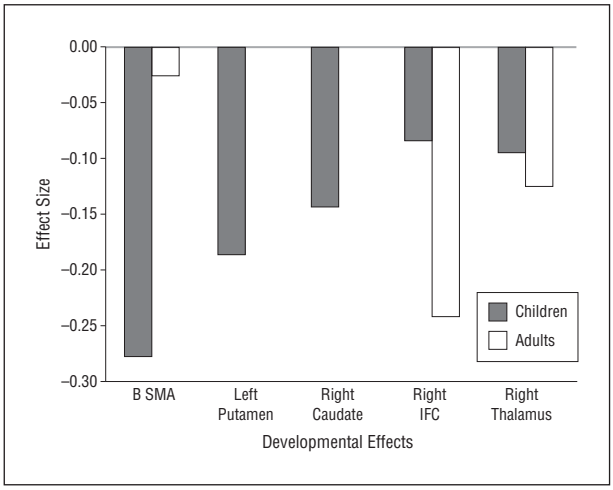

Figure 4. Age group analysis for regions that differed in patients with attention-deficit/hyperactivity disorder relative to healthy controls during inhibition shows that the reduced activation in the supplementary motor area (SMA), in the left putamen and globus pallidus, and in the right caudate was abnormal only in children with attention-deficit/hyperactivity disorder relative to their age-matched healthy controls, while the reduced activation in the right inferior prefrontal cortex (IFC) and in the right thalamus was significant only in adults with attention-deficit/hyperactivity disorder relative to their age-matched healthy controls. B indicates bilateral.

trol, in the right IFC, reaching into the anterior insula, SMA and ACC, left caudate, and thalamus. For attention functions, patients with ADHD showed consistent deficits in a different fronto-basal ganglia-parieto-cerebellar network that is typical for visuospatial attention, including the right DLPFC, left putamen and right posterior thalamus, caudate tail, and parietal areas, with enhanced cerebellar activation. Furthermore, long-term stimulant medication use was associated with more normal function in the right caudate during attention tasks and at a trend level during interference inhibition. The findings suggest that long-term stimulant medication use is associated with more normal basal ganglia function, in line with documented effects of more normal basal ganglia structure.[37,51] Age effects could not be tested for attention due to small numbers of adult studies. For the inhibition domain, the linear age meta-regression was not significant, but a categorical comparison showed that basal ganglia and SMA deficits were observed only in children with ADHD, while the right IFC or insula and thalamus deficits were significant only in adults with ADHD relative to controls.

INHIBITION META-ANALYSIS

The reduced activation in patients with ADHD relative to controls in the right inferior frontal junction reaching into insula, SMA or ACC, left caudate head, and right thalamus suggests deficits in a typical adult and adolescent inhibitory network for motor response and interference inhibition,[40,44,47,90-92] in line with individual studies.[12,16,32,86,93] The more restricted right IFC and insula deficit finding narrows the wider bilateral IFC and DLPFC deficit findings of a previous meta-analysis[38] of inhibition functions. The underfunctioning of the right inferior frontal junction or insula in particular is one of the most consistent deficits in the ADHD FMRI literature of inhibition,[4] which may be a disorder-specific neurofunctional biomarker for ADHD[4] relative to patients with conduct disorder[25,27] and obsessive-compulsive disorder.[10]

While the right IFC or insula was underactivated during both inhibition domains, supporting a more generic role of the inferior frontal junction in motor or interference inhibition,[40,94] the deficits in the ACC and SMA showed inhibitory domain-specific dysfunctions. The SMA, a key area for motor response inhibition,[40,92] was dysfunctional only during motor response inhibition. The cognitive division of the ACC, crucial for interference and conflict inhibition,[89,95] was underactivated during both tasks, but in the left hemisphere for interference inhibition and in a more right hemispheric location during motor inhibition.

ATTENTION META-ANALYSIS

During attention tasks, patients with ADHD showed consistently reduced activation in a different fronto-basal ganglia-thalamo-parietal network, in line with prior literature comprising the right DLPFC,[19,23,25,27,29,35] left putamen and globus pallidus, right thalamic pulvinar and caudate tail,‡ and inferior parietal lobe and precuneus.[5,9,23,24,28,29,87,88] These regions form part of a visuospatial attention network, whereby posterior parietal, precuneus, and the thalamic pulvinar regions mediate the representation of and orienting toward spatial locations, while the anterior DLPFC is responsible for target detection and selective attention, alerting, and switching attention.[49,96] The findings of domain-dissociated deficits in distinct IFC and SMA fronto-striato-thalamic and

‡*References 18, 23, 24, 26, 28, 29, 35, 87, 88.*

DLPFC fronto-basal ganglia-thalamo-parietal networks in patients with ADHD during inhibition and attention, respectively, support the notion of multisystem deficits in ADHD,[4,35,97] compromising different fronto-basal ganglia-parieto-cerebellar networks that mediate at least 2 functional domains.

The dissociated but right hemispheric DLPFC and IFC deficits in ADHD for both cognitive domains support previous meta-analytical structural findings of high effect sizes for right frontal deficits in patients with ADHD.[98] These results are in line with theories of predominantly right hemispheric deficits.[99]

The enhanced activation in patients with ADHD relative to controls in the cerebellum and occipital lobe during attention functions may reflect compensatory enhanced activation of the posterior part of a DLPFC–cerebellar network for sustained attention.[49,100] This is supported by individual sustained attention FMRI studies[25,35] that found that enhanced cerebellum activation in ADHD was anticorrelated with reduced prefrontal activation that correlated with attention performance, suggesting compensation. The finding of enhanced cerebellar activation during attention functions contrasts with evidence for reduced cerebellar activation during timing functions.[69,101-103] It reinforces the notion that brain dysfunctions in ADHD, as well as the direction of their abnormality, appear to be task dependent, with different fronto-basal ganglia-parieto-cerebellar neural networks being deficient in patients with ADHD in the context of different cognitive domains.

The findings support recent neurobiological theories of ADHD that suggest that the disorder is multisystemic, characterized by multiple parallel deficits in several fronto-striatal, fronto-cortical, and fronto-cerebellar networks that mediate the different cognitive functions that are impaired in the disorder.[4,35,97,104,105] Within the inhibitory domain, the findings reconcile theories of predominant IFC,[4] ACC,[106] and SMA deficits[86] in ADHD, by showing that SMA deficits are specifically related to motor response inhibition, while IFC and ACC dysfunctions underlie both motor and interference inhibition. While in this study we have delineated the different fronto-basal ganglia-parietal networks that are deficient for attention and inhibition functions, future meta-analysis studies should investigate potential fronto-cortical and fronto-subcortical neural network deficiencies during other tasks such as timing[102] and reward-associated functions.[4]

EFFECT OF LONG-TERM STIMULANT MEDICATION USE

The meta-regression analysis for attention showed that long-term stimulant medication use (for periods ranging from 6 months to 3 years) was associated with more normal right but not left caudate function, and this survived age correction. The results parallel previous meta-analysis findings of normal right caudate structure in a similar location (Talairach *x*, *y*, and *z* coordinates of 16, 2, and 20) in patients with long-term medication relative to never-medicated patients and controls.[37] Together, they suggest a right-lateralized positive plastic effect of long-term stimulant medication use on basal ganglia structure and function. The gradual normalization of right caudate function with long-term stimulant medication use may also be related to meta-analytic positron emission tomography findings of higher striatal dopamine transporter levels in patients with long-term medication use relative to controls and medication-naive patients, who had reduced striatal dopamine transporter levels relative to controls.[107] The right-lateralized effect may also explain why long-term stimulant medication use did not normalize the abnormal caudate function in the meta-regression analysis of the inhibition tasks, which was left hemispheric, as is typical for motor inhibition tasks.[6,12] Furthermore, a right-lateralized effect would be in line with the trend-level finding toward an association between long-term stimulant medication use and more normal right caudate activation in the interference inhibition tasks, which may not have reached statistical significance due to lack of power. This would also echo evidence that methylphenidate has a stronger effect on right basal ganglia blood flow and metabolism, rather than left.[108,109]

However, the significant meta-regression finding for the association between long-term stimulant medication use and right caudate activation for the attention meta-analysis should be considered preliminary and be interpreted with caution given that it was based on 37 medicated patients, which were only 21.6% of the entire sample of 171 patients. Also, the association between long-term stimulant medication use and more normal striatal activation was observed only at a trend level for the interference inhibition regression analysis, which was also underpowered. In addition, while there was a significant linear association, the correlation figure is not suggestive of a linear dose-response effect.

EFFECT OF AGE

Linear age effects could not be tested for the attention domain because there were only 2 adult studies. While linear age effects on brain activation were not observed for the inhibition meta-regression analysis, a categorical age group meta-analysis showed that basal ganglia and SMA or ACC underactivation was more prominently associated with pediatric ADHD, while IFC-thalamic deficits were more pronounced in adult ADHD relative to their age-matched controls. The findings are in line with structural findings of normal basal ganglia gray matter in adults with ADHD relative to children with ADHD, who had reduced basal ganglia gray matter relative to controls.[37] The results are also in line with longitudinal data in ADHD showing normalization of basal ganglia structural deficits in early adulthood.[53] Together, these data suggest that basal ganglia deficits may normalize in ADHD adulthood, while frontal deficits may become more prominent, in line with theories that suggest that frontal lobe deficits in ADHD may be secondary to primary subcortical deficits.[110]

Overall, the findings illustrate that age, long-term stimulant medication use, and differences in the cognitive domain tested all have important effects on the brain activation deficits in patients with ADHD. Future stud-

ies need to bear this in mind as follows: (1) by including only medication-naive patients with ADHD to assess ADHD pathology and not potential brain-adaptive responses to long-term stimulant medication use (or at least to test for medication effects in subgroups of medicated and medication-naive samples in sufficiently large sample sizes), (2) by assessing narrowly defined and homogeneous age groups for a better stratification of ADHD deficits according to age groups, and (3) by using similar comparable cognitive tasks to elucidate deficits in specific cognitive domains.

LIMITATIONS

This study has several limitations, inherent to all meta-analyses. First, peak-based meta-analyses are based on coordinates from published studies, rather than raw statistical brain maps, providing less accurate results.[58] Second, different studies used different statistical thresholds. Third, while voxelwise meta-analytical methods provide excellent control for false-positive results, it is more difficult to avoid false-negative results.[58] Fourth, regression in voxel-based meta-analyses should be considered with caution; however, spurious results were minimized herein by using more conservative thresholds and by reporting only those findings that were significant both when comparing medicated vs unmedicated patients and patients vs controls. We were able to combine similar tasks for the inhibition domain, and there were a sufficient number of studies to further subdivide articles into motor and interference inhibition sub–meta-analyses. However, for the attention domain, fewer FMRI studies were available on a larger range of different tasks, so that we had to combine tasks of a range of different visuospatial attention domains, including selective, sustained, and flexible attention. Future meta-analytic studies should subcategorize the attention domain into more homogeneous attention tasks once the field of FMRI of attention functions in ADHD has expanded. Fifth, we conducted a meta-analysis of only inhibition and attention studies, and future meta-analyses will need to investigate other compromised functions such as timing[102] and motivation.[4]

In conclusion, patients with ADHD have cognitive domain–specific dissociated dysfunctions in distinct fronto-basal ganglia-thalamic networks, involving the right IFC, SMA, and anterior caudate for inhibition functions and the right DLPFC, posterior basal ganglia, and parietal areas for attention functions. Furthermore, long-term stimulant medication use appears to be associated with a gradual normalization of right caudate deficits during attention.

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Author Affiliations: Departments of Child and Adolescent Psychiatry (Drs Hart and Rubia) and Psychosis Studies (Drs Radua, Nakao, and Mataix-Cols), Institute of Psychiatry, King's College London, London, England; Department of Neuropsychiatry, Graduate School of Medical Sciences, Kyushu University, Kyushu, Japan (Dr Nakao); and Research Unit, Fundació per a la Investigació i la Docència Maria Angustias Giménez–Centro de Investigación Biomédica en Red de Salud Mental, Sant Boi de Llobregat, Barcelona, Spain (Dr Radua).
Correspondence: Katya Rubia, PhD, Department of Child and Adolescent Psychiatry, Institute of Psychiatry, King's College London, Social Genetic and Developmental Psychiatry Center, PO Box 46, De Crespigny Park, London SE5 8AF, England (katya.rubia@kcl.ac.uk).
Author Contributions: Dr Hart performed the statistical analysis, with help from Dr Radua, and had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr Hart took responsibility for writing the "Methods" and "Results" sections, and Dr Rubia wrote the introduction and the "Comment" section, both of them with contributions from coauthors.
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