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.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) is one of the most debilitating childhood disorders, defined by age-inappropriate impulsiveness, inattention, and hyperactivity, persisting into adulthood in about 65% of cases. Patients with ADHD have consistent deficits in motor response and interference inhibition, as well as in attention, in particular selective, sustained, and flexible attention. 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 and stop tasks and in the bilateral IFC, anterior cingulate cortex (ACC), basal ganglia, and parieto-temporal regions during interference inhibition tasks. 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 regions during inhibition tasks.

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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

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individual 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 r 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,55-56 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, intra-study variability, and between-study heterogeneity.56

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.
Table 1. Inhibition Tasks

<table>
<thead>
<tr>
<th>Source</th>
<th>Task</th>
<th>Patients With ADHD</th>
<th>Healthy Controls</th>
<th>Brain Regions Activated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. (% Male)</td>
<td>Mean Age, y</td>
<td>Controls &gt; ADHD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean Age, y</td>
<td>% Medicated</td>
<td>% Comorbidities</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Time Stopped, h)</td>
<td>(Type)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Motor Inhibition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Booth et al.5</td>
<td>GNG</td>
<td>12 (66.7) 11</td>
<td>100 (48)</td>
<td>0</td>
</tr>
<tr>
<td>Dibbets et al.8</td>
<td>GNG</td>
<td>16 (100) 28.9</td>
<td>87.5 (24)</td>
<td>0</td>
</tr>
<tr>
<td>Durston et al.6</td>
<td>GNG</td>
<td>7 (85.7) 8.55</td>
<td>100 (24)</td>
<td>?</td>
</tr>
<tr>
<td>Durston et al.12</td>
<td>GNG</td>
<td>11 (100) 13.97</td>
<td>54.5 (24)</td>
<td>27.27 (ODD)</td>
</tr>
<tr>
<td>Karch et al.11</td>
<td>GNG</td>
<td>8 (87.5) 38.3</td>
<td>0</td>
<td>8 (87.5) 37.8</td>
</tr>
<tr>
<td>Koosstra et al.9</td>
<td>GNG</td>
<td>11 (100) 21.5</td>
<td>0</td>
<td>11 (100) 22.3</td>
</tr>
<tr>
<td>Smith et al.6</td>
<td>GNG</td>
<td>17 (100) 12.8</td>
<td>0</td>
<td>29.41 (CD)</td>
</tr>
<tr>
<td>Spinelli et al.18</td>
<td>GNG</td>
<td>13 (69.2) 10.6</td>
<td>15.4 (48)</td>
<td>23.07 (ODD, simple phobia)</td>
</tr>
<tr>
<td>Suskauer et al.10</td>
<td>GNG</td>
<td>25 (60) 10.8</td>
<td>75 (48)</td>
<td>56 (ODD, simple phobia)</td>
</tr>
<tr>
<td>Tamm et al.13</td>
<td>GNG</td>
<td>10 (100) 16.0</td>
<td>50 (18)</td>
<td>12 (100) 15.58</td>
</tr>
<tr>
<td>Cubillo et al.15</td>
<td>Stop</td>
<td>11 (100) 29</td>
<td>0</td>
<td>77 (Anxiety, mood, CD, SA)</td>
</tr>
<tr>
<td>Passarotti et al.16</td>
<td>Stop</td>
<td>11 (54.55) 13.09</td>
<td>53 (1 wk)</td>
<td>0</td>
</tr>
<tr>
<td>Rubia et al.17</td>
<td>Stop</td>
<td>16 (100) 13</td>
<td>0</td>
<td>31.25 (CD)</td>
</tr>
<tr>
<td>Rubia et al.18</td>
<td>Stop</td>
<td>7 (100) 15.71</td>
<td>0</td>
<td>42.86 (CD)</td>
</tr>
<tr>
<td>Rubia et al.19</td>
<td>Stop</td>
<td>12 (100) 13</td>
<td>0</td>
<td>8.33 (ODD, CD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Interference Inhibition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cubillo et al.20</td>
<td>Simon</td>
<td>11 (100) 29</td>
<td>0</td>
<td>77 (Anxiety, mood, CD, SA)</td>
</tr>
<tr>
<td>Rubia et al.21</td>
<td>Simon</td>
<td>12 (100) 13</td>
<td>0</td>
<td>8.33 (ODD/CD)</td>
</tr>
<tr>
<td>Rubia et al.22</td>
<td>Simon</td>
<td>18 (100) 14.25</td>
<td>0</td>
<td>5.55 (CD)</td>
</tr>
<tr>
<td>Banich et al.23</td>
<td>Stroop</td>
<td>23 (60.8) 20.0</td>
<td>87.0 (24)</td>
<td>0</td>
</tr>
<tr>
<td>Burgess et al.24</td>
<td>Stroop</td>
<td>20 (60) 20.1</td>
<td>65 (24)</td>
<td>0</td>
</tr>
<tr>
<td>Peterson et al.25</td>
<td>Stroop</td>
<td>16 (81.2) 13.1</td>
<td>0</td>
<td>32.25 (Depression, ODD, specific phobias, SAD, GAD)</td>
</tr>
</tbody>
</table>

Abbreviations: ACC, anterior cingulate cortex; ADHD, attention-deficit/hyperactivity disorder; B, bilateral; CD, conduct disorder; GAD, general anxiety disorder; 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.
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>
<thead>
<tr>
<th>Source</th>
<th>Task</th>
<th>Patients With ADHD</th>
<th>Healthy Controls</th>
<th>Brain Regions Activated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (% Male)</td>
<td>Mean Age, y</td>
<td>% Medicated (Time Stopped)</td>
<td>% Comorbidities (Type)</td>
</tr>
<tr>
<td>Cao et al, 2008</td>
<td>Cued target detection</td>
<td>12 (100)</td>
<td>14.9</td>
<td>0</td>
</tr>
<tr>
<td>Rubia et al, 2007</td>
<td>Oddball</td>
<td>17 (100)</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Tamm et al, 2007</td>
<td>Oddball</td>
<td>14 (100)</td>
<td>15.6</td>
<td>0</td>
</tr>
<tr>
<td>Cubillo et al, 2011</td>
<td>Oddball</td>
<td>11 (100)</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>Rubia et al, 2009</td>
<td>Oddball</td>
<td>20 (100)</td>
<td>13.2</td>
<td>0</td>
</tr>
<tr>
<td>Cubillo et al, 2012</td>
<td>CPT</td>
<td>11 (100)</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>Rubia et al, 2009</td>
<td>CPT</td>
<td>18 (100)</td>
<td>13.3</td>
<td>0</td>
</tr>
<tr>
<td>Rubia et al, 2009</td>
<td>CPT</td>
<td>13 (100)</td>
<td>12.5</td>
<td>0</td>
</tr>
<tr>
<td>Konrad et al, 2007</td>
<td>Alerting, orienting</td>
<td>9 (100)</td>
<td>11.1</td>
<td>0</td>
</tr>
<tr>
<td>Booth et al, 2005</td>
<td>Selective and divided attention</td>
<td>12 (66.7)</td>
<td>11</td>
<td>100 (48h)</td>
</tr>
<tr>
<td>Shafritz et al, 2004</td>
<td>Selective and divided attention</td>
<td>15 (73.3)</td>
<td>15.1</td>
<td>53.3 (?)</td>
</tr>
<tr>
<td>Silk et al, 2005</td>
<td>Mental rotation task</td>
<td>7 (100)</td>
<td>14.38</td>
<td>0</td>
</tr>
<tr>
<td>Vance et al, 2007</td>
<td>Mental rotation task</td>
<td>12 (100)</td>
<td>11.1</td>
<td>0</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Contrast</th>
<th>All Inhibition Tasks Together</th>
<th>Motor Inhibition</th>
<th>Interference Inhibition</th>
<th>All Attention Tasks Together</th>
<th>Effect of Stimulant Medication History</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Taalair x, y, z Coordinates</td>
<td>Signed Differential Mapping z Score</td>
<td>P Value</td>
<td>No. of Voxels</td>
<td>Breakdown (No. of Voxels)</td>
</tr>
<tr>
<td>Healthy controls &gt; patients with ADHD</td>
<td>Left and right SMA/ACC</td>
<td>-2, 6, 48</td>
<td>-2.568</td>
<td>&lt;.001</td>
<td>726</td>
</tr>
<tr>
<td>Right IFC/anterior insula</td>
<td>40, 16, 4</td>
<td>-1.869</td>
<td>&lt;.001</td>
<td>225</td>
<td>Right BA 47/45 (151), right insula (33), right BA 44 (20), right BA 45 (17)</td>
</tr>
<tr>
<td>Left caudate head/putamen/anterior insula</td>
<td>-24, -4, 16</td>
<td>-1.485</td>
<td>&lt;.001</td>
<td>82</td>
<td>Left caudate head/insula (22), left caudate head (26), left putamen (32)</td>
</tr>
<tr>
<td>Right thalamus</td>
<td>6, -18, 4</td>
<td>-1.381</td>
<td>.001</td>
<td>89</td>
<td>. . .</td>
</tr>
<tr>
<td>Healthy controls &gt; patients with ADHD</td>
<td>Right SMA/ACC</td>
<td>4, 10, 48</td>
<td>-2.580</td>
<td>&lt;.001</td>
<td>644</td>
</tr>
<tr>
<td>Right IFC/insula</td>
<td>36, 18, 8</td>
<td>-1.826</td>
<td>&lt;.001</td>
<td>111</td>
<td>Right BA 45/47/insula (85), right BA 44 (10)</td>
</tr>
<tr>
<td>Right thalamus</td>
<td>4, -16, 4</td>
<td>-1.728</td>
<td>&lt;.001</td>
<td>123</td>
<td>. . .</td>
</tr>
<tr>
<td>Left caudate head</td>
<td>-16, -8, 22</td>
<td>-1.461</td>
<td>.003</td>
<td>12</td>
<td>. . .</td>
</tr>
<tr>
<td>Right fusiform gyrus</td>
<td>26, -58, -8</td>
<td>-1.557</td>
<td>.002</td>
<td>26</td>
<td>Right BA 19</td>
</tr>
<tr>
<td>Healthy controls &gt; patients with ADHD</td>
<td>Right ACC</td>
<td>-2, 2, 40</td>
<td>-1.141</td>
<td>&lt;.001</td>
<td>75</td>
</tr>
<tr>
<td>Right IFC/insula</td>
<td>46, 14, -4</td>
<td>-1.127</td>
<td>&lt;.001</td>
<td>108</td>
<td>Right BA 47/insula (49), right BA 47 (30), right BA 45 (10)</td>
</tr>
<tr>
<td>Right caudate head</td>
<td>16, -14, 22</td>
<td>-1.022</td>
<td>.002</td>
<td>11</td>
<td>. . .</td>
</tr>
<tr>
<td>Left posterior insula/parietal lobe</td>
<td>-36, -22, 29</td>
<td>-1.085</td>
<td>.002</td>
<td>39</td>
<td>Left BA 13/40</td>
</tr>
<tr>
<td>Healthy controls &gt; patients with ADHD</td>
<td>Right middle frontal (DLFPC)</td>
<td>26, 28, 44</td>
<td>-1.429</td>
<td>.002</td>
<td>46</td>
</tr>
<tr>
<td>Left putamen/pallidus</td>
<td>-22, 0, -2</td>
<td>-2.091</td>
<td>&lt;.001</td>
<td>658</td>
<td>Left putamen (414), left pallidum (188), left caudate (19)</td>
</tr>
<tr>
<td>Right thalamus (pulvinar)/caudate tail/posterior insula</td>
<td>20, -26, 16</td>
<td>-1.523</td>
<td>.001</td>
<td>101</td>
<td>Right thalamus/pulvinar (40), right posterior insula (36), right caudate (19)</td>
</tr>
<tr>
<td>Right inferior parietal</td>
<td>26, -48, 44</td>
<td>-1.690</td>
<td>&lt;.001</td>
<td>74</td>
<td>Right BA 40 (47), right BA 7 (22)</td>
</tr>
<tr>
<td>Right precuneus</td>
<td>4, -54, 38</td>
<td>-1.367</td>
<td>.003</td>
<td>30</td>
<td>Right BA 7</td>
</tr>
<tr>
<td>Right superior temporal</td>
<td>58, -10, 12</td>
<td>-1.338</td>
<td>.003</td>
<td>19</td>
<td>Right BA 42 (10)</td>
</tr>
<tr>
<td>Patients with ADHD &gt; healthy controls</td>
<td>Right cerebellum</td>
<td>12, -72, -14</td>
<td>1.436</td>
<td>&lt;.001</td>
<td>372</td>
</tr>
<tr>
<td>Left cerebellum</td>
<td>-12, -76, 16</td>
<td>1.256</td>
<td>&lt;.001</td>
<td>125</td>
<td>Left BA 15 (81), left BA 17 (27)</td>
</tr>
<tr>
<td>Unmedicated patients &lt; long-term medicated patients and healthy controls</td>
<td>Right caudate tail</td>
<td>20, -26, 20</td>
<td>1.646</td>
<td>&lt;.001</td>
<td>69</td>
</tr>
<tr>
<td>Right caudate tail</td>
<td>20, -26, 20</td>
<td>1.646</td>
<td>&lt;.001</td>
<td>69</td>
<td>. . .</td>
</tr>
<tr>
<td>Long-term medicated patients &lt; healthy controls</td>
<td>Left cerebellum</td>
<td>-22, -54, -16</td>
<td>-2.176</td>
<td>&lt;.001</td>
<td>254</td>
</tr>
</tbody>
</table>

Abbreviations: ACC, anterior cingulate cortex; ADHD, attention-deficit/hyperactivity disorder; BA, Brodmann area; DLFPC, 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 ($r = 0.233, \text{permutation-derived } P < .001$), 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).
This meta-analysis across FMRI studies of inhibition and attention functions shows task domain-specific, disso-
ciated 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 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.
control, 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 use is associated with more normal basal ganglia function, in line with documented effects of more normal basal ganglia structure. 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-thalamo-parietal network, in line with prior literature comprising the right DLPFC, left putamen and globus pallidus, right thalamic pulvinar and caudate tail, and inferior parietal lobe and precuneus, were dysfunctional only during motor response inhibition. The cognitive division of the ACC, crucial for interference and conflict inhibition, 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, left putamen and globus pallidus, right thalamic pulvinar and caudate tail, and inferior parietal lobe and precuneus. 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. The findings of domain-dissociated deficits in distinct IFC and SMA fronto-striato-thalamic and
functions that are impaired in the disorder.4,35,97,104,105 cerebellar networks that mediate the different cognitive
eral fronto-striatal, fronto-cortical, and fronto-
temic, characterized by multiple parallel deficits in sev-
neral cognitive domains.

The dissociated but right hemispheric DLPFC and IFC
deficits in ADHD for both cognitive domains support pre-
vious 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 rela-
tive to controls in the cerebellum and occipital lobe dur-
ing attention functions may reflect compensatory en-
hanced activation of the posterior part of a
DLPFC–cerebellar network for sustained attention.49,100 This is supported by individual sustained attention FMRI
studies95,97 that found that enhanced cerebellum activa-
tion in ADHD was anticorrelated with reduced prefron-
tal activation that correlated with attention perform-
ance, suggesting compensation. The finding of enhanced
cerebellar activation during attention functions con-
trasts with evidence for reduced cerebellar activation dur-
ing timing functions.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 dif-
f erent fronto-basal ganglia-pario-cerebellar neural net-
works being deficient in patients with ADHD in the con-
text of different cognitive domains.

The findings support recent neurobiological theories
of ADHD that suggest that the disorder is multisys-
temic, characterized by multiple parallel deficits in sev-
eral 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 theo-
ries of predominant IFC,4 ACC,106 and SMA deficits86 in
ADHD, by showing that SMA deficits are specifically re-
lated to motor response inhibition, while IFC and ACC
dysfunctions underlie both motor and interference in-
hibition. While in this study we have delineated the dif-
f erent fronto-basal ganglia-pario-cerebellar networks that are
deficient for attention and inhibition functions, future
meta-analysis studies should investigate potential fronto-
cortical and fronto-subcortical neural network deficien-
cies during other tasks such as timing102 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 rang-
ing from 6 months to 3 years) was associated with more
normal right but not left caudate function, and this sur-
vived 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 rela-
tive to never-medicated patients and controls.35 To-
gether, they suggest a right-lateralized positive plastic ef-
f ect 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 emis-
tomography findings of higher striatal dopamine
transporter levels in patients with long-term medica-
tion use relative to controls and medication-naive pa-
tients, 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.5,112 Furthermore, a right-lateralized effect would be in line
with the trend-level finding toward an association be-
tween long-term stimulant medication use and more nor-
mal right caudate activation in the interference inhibi-
tion 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 en-
tire sample of 171 patients. Also, the association be-
tween long-term stimulant medication use and more nor-
mal 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 categori-
cal age group meta-analysis showed that basal ganglia
and SMA or ACC underactivation was more prominently
associated with pediatric ADHD, while IFC-thalamic defi-
cits 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 struc-
tural deficits in early adulthood.53 Together, these data
suggest that basal ganglia deficits may normalize in ADHD
adulthood, while frontal deficits may become more promi-
nent, in line with theories that suggest that frontal lobe
deficits in ADHD may be secondary to primary subcor-
tical deficits.110

Overall, the findings illustrate that age, long-term
stimulant medication use, and differences in the cogni-
tive 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. 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. 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 we were able 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 and motivation.

In conclusion, patients with ADHD have cognitive domain–specific disassociated 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.

**REFERENCES**


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