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Functional Decoding and Meta-Analytic Connectivity Modeling in Adult Attention-Deficit/Hyperactivity Disorder

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Abstract

Background—Task-based fMRI studies of adult Attention-Deficit/Hyperactivity Disorder (ADHD) have revealed various ADHD-related dysfunctional brain regions, with heterogeneous findings across studies. Here, we used novel meta-analytic data-driven approaches to characterize the function and connectivity profile of ADHD-related dysfunctional regions consistently detected across studies.

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Methods—We first conducted an activation likelihood estimation (ALE) meta-analysis of 24 task-based fMRI studies in adults with ADHD. Each ADHD-related dysfunctional region resulting from the ALE meta-analysis was then analyzed using *functional decoding* based on ~7,500 fMRI experiments in the *BrainMap* database. This approach allows mapping brain regions to functions not necessarily tested in individual studies, thus suggesting possible novel functions for those regions. Additionally, ADHD-related dysfunctional regions were clustered based on their functional co-activation profiles across all the experiments stored in *BrainMap* (*meta-analytic connectivity modeling*).

Results—ADHD-related hypoactivation was found in left putamen, left inferior frontal gyrus (pars opercularis), left temporal pole, and right caudate. Functional decoding mapped the left putamen and the left temporal lobe to cognitive aspects of music perception/reproduction and language semantics, respectively; both these regions clustered together based on their meta-analytic functional connectivity. Left inferior gyrus mapped to executive function tasks; right caudate mapped both to executive functions tasks and music-related processes.

Conclusions—Our study provides meta-analytic support to the hypothesis that, in addition to well-known deficits in typical executive functions, impairment in processes related to music perception/reproduction and language semantics may be involved in the pathophysiology of adult ADHD.

Keywords

Attention-Deficit/Hyperactivity Disorder; fMRI; meta-analysis; meta-analytic connectivity modelling; functional decoding; adults

Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder (1), with an estimated prevalence of about 5% in school-aged children (2). Although ADHD was previously thought to fully remit in adolescence, evidence shows that impairing ADHD symptoms persist into adulthood in a substantial proportion of cases (3) and the estimated prevalence of adult ADHD is about 2.5% (4).

A growing neuroimaging literature has addressed the neuronal correlates of adult ADHD via task-based functional MRI (fMRI). Given the analytical flexibility of fMRI studies (e.g., diverse statistical software and approaches across studies), generally small sample sizes and heterogeneity in sample characteristics (e.g., sex ratio, psychiatric comorbidities) (5), it may not surprise that findings from task-based fMRI studies in adults with ADHD have been somewhat inconsistent. This raises the question of the possible utility of meta-analytic tools. In a meta-analysis of 16 studies examining a diverse set of neuropsychological tasks (6), Cortese et al. found adult ADHD-related hypoactivation in the right central sulcus, precentral gyrus, and middle frontal gyrus and ADHD-related hyperactivation in the right angular and middle occipital gyri. In a meta-analysis of studies in children and adults, Hart et al. (7) found ADHD-related hypoactivation in right inferior frontal cortex, supplementary motor area, anterior cingulate cortex, and striato-thalamic areas, when pooling studies on inhibition, and ADHD-related hypoactivation in right dorsolateral prefrontal cortex,

posterior basal ganglia, thalamic and parietal regions when focusing on attention tasks. In another meta-analysis focused on timing tasks, including studies both in children and adults, Hart et al. (8) found ADHD-related hypoactivation in the cerebellar vermis, left inferior prefrontal cortex and insula, and in left supramarginal gyrus extending into left superior temporal and postcentral gyri. They also found ADHD-related hyperactivation in bilateral precuneus extending to cuneus and posterior cingulate cortex. McCarthy et al. (9) meta-analyzed four studies in adults (10–13) using the Go/No-Go task and showed ADHD-related hypoactivation in left medial frontal gyrus and right inferior parietal lobule, although these results should be considered with caution as those analyses were likely underpowered. Finally, Lei et al. (14) pooled seven studies of motor inhibition in adults and found ADHD-related hypoactivation in right insula, right caudate, and right lentiform nucleus and significantly increased activation in right inferior occipital gyrus, right precuneus, and right superior parietal lobule.

Given the number of studies published in the intervening four years, we first performed an updated meta-analysis of adult ADHD task-based fMRI studies. In addition, we aimed to address the “reverse inference problem,” i.e., inferring the engagement and aberration of specific mental processes from patterns of brain activations, which remains an issue when interpreting results of individual task-based fMRI studies as well as their meta-analyses (15). For example, if a brain region is unselectively activated during many different tasks, activation in that region provides little information regarding specific mental process that may be disturbed in patients (15). Strategies to potentially overcome this problem have been recently provided by large-scale databases of fMRI studies, such as *BrainMap* (16) or *Neurosynth* (17). Emerging approaches leverage these databases to perform *functional decoding* of brain regions and infer their interaction patterns using *meta-analytic connectivity modeling* (MACM). *Functional decoding* is a data-driven approach that provides quantitative inference on the mental processes related to a specific brain region (18) by investigating the association between activation in that region and mental processes across a large number of fMRI studies of healthy subjects stored in large databases. *Meta-analytic connectivity modeling* (19) is another data-driven method to assess the functional co-activation between a particular region-of-interest and all other voxels in the brain. Regions with similar co-activation profiles can then be identified through cluster analysis (20;21).

Here, to gain insight into the pathophysiology of ADHD in adults, we: 1) updated a meta-analysis (6) of task-based fMRI studies of adults with ADHD conducted in 2011; 2) functionally decoded the identified ADHD-related hypo or hyperactivated regions; 3) characterized, using MACM, significant co-activation patterns of each ADHD-related hypo or hyperactivated region resulting from the updated meta-analysis; and 4) clustered ADHD-related hypo or hyperactivated regions, based on their co-activation patterns, to identify possible dysfunctional sub-networks in adult ADHD.

Given the potential effects of comorbid psychiatric disorders and stimulant treatment on brain activation during fMRI tasks, we also sought to conduct sub-group analyses taking into account the effect of comorbidity and stimulant treatment.

Methods and Materials

Search strategy

Cortese et al. (6) included 16 studies in adults, published up to June 30, 2011. We updated this meta-analysis (last search on March 15, 2015) using the same search strategy, as detailed in the Supplement.

Study eligibility criteria

Studies were retained if: 1) they presented data on adults with ADHD; 2) ADHD diagnosis was made according to DSM or ICD; 3) a matched group of healthy subjects was included; 4) data were reported as 3-D coordinates in stereotactic space; and 5) between-group contrasts were included. Studies were excluded if: 1) a neuroimaging method other than fMRI was used; 2) they were based on participants without a formal diagnosis of ADHD; 3) they assessed the effect of medication without reporting fMRI data at baseline or after wash-out; 4) they reported only within-group contrasts; 5) they reported only *a priori* region-of-interest analyses (as these violate the assumption that the likelihood of locating activated foci is equal at every voxel under the null hypothesis); or 6) they included adults with ADHD in partial remission, since these may represent a neurobiologically distinct entity.

Planned meta-analyses

As previously (6;22), we first performed a meta-analysis of ADHD-related hypo- or hyperactivated regions, regardless of task type, to identify regions that are consistently dysfunctional across studies. We used activation likelihood estimation (ALE) (23). We also explored the possibility of conducting subgroup meta-analyses focused on specific task types (e.g., inhibition or attention). Additionally, we aimed to conduct a subgroup analysis including only studies where participants did not have comorbid psychiatric disorders. Finally, we planned a sub-group analysis including only studies with stimulant-naïve participants. When exploring the feasibility of such sub-group meta-analyses, we considered that ALE meta-analyses are conceptually valid and statistically robust when at least 15 experiments (i.e., contrasts) are pooled (24).

ALE meta-analytic technique

First, coordinates reported in Talairach space were transformed to MNI coordinates using the icbm2tal (Lancaster) transformation (25). Afterwards, ALE was used to identify areas showing a convergence of coordinates across experiments. We used random-effects inference. Taking the union across MA maps yielded voxel-wise ALE scores describing the convergence of results at each particular brain location. To distinguish *true* convergence between studies from *random* convergence (i.e., noise), ALE scores were compared to a null-distribution (26) reflecting random spatial association between experiments. The p-value of these ALE scores is given by the proportion of equal or higher values obtained under the null-hypothesis (26). The ensuing p-values for each meta-analysis were then thresholded using Threshold-Free Cluster Enhancement (TFCE, corrected of $p < 0.05$). All analyses were run using in-house MATLAB scripts implementing the ALE algorithm as described previously (27–29).

Functional decoding

Studies stored in BrainMap are individually coded by a first investigator and cross-validated by a second investigator, yielding rigorous labelling. Studies are coded in terms of *Behavioral domain* and *Paradigm class*. *Behavioral domains* (30) include the following main categories: *Cognition*, *Action*, *Perception*, *Emotion*, and *Interoception*, as well as their related sub-categories (e.g., *Memory* is a subcategory of *Cognition*; *Working memory* is a subcategory of *Memory*). *Paradigm classes* categorize the specific task employed, such as *n-back* (see <http://brainmap.org/scribe/> for the complete BrainMap taxonomy). We only considered studies from BrainMap reporting experiments (within-group contrasts between two experimental conditions) on healthy subjects, yielding approximately 7,500 task-based experiments at time of analysis (16). To avoid pre-selection bias, we considered all eligible BrainMap experiments regardless of their behavioral categories. We chose BrainMap as a reference rather than Neurosynth (17), because the latter is based on automated text-mining and, as such, has the drawback that different contrasts or experiments within a paper can usually not be separated. As shown (31–33), when not directly reflecting functions that were specifically tested in individual studies included in the meta-analysis, data-driven functional decoding may generate new hypotheses, i.e., additional possible relevant functions of the identified regions. Nevertheless, these should not be considered as the *exclusive* functions of those particular regions. Further details on functional decoding methods are reported in the Supplement.

Meta-analytic connectivity modeling (MACM) and clustering

The functional co-activation of each ADHD-related hyper- or hypoactivated region resulting from the ALE meta-analysis was determined by MACM. This approach assesses which brain regions are co-activated above chance with a particular seed region (here, each significant brain region resulting from the ALE meta-analysis) across the pool of experiments in healthy subjects stored in BrainMap. Finally, we used multivariate clustering to delineate similarities and differences among the whole-brain co-activation patterns of meta-analytically derived regions. We applied *multidimensional scaling (MDS)* with Sammon's nonlinear mapping as the goodness-of-fit criterion (34). Further details are reported in the Supplement.

Results

Literature search

We found 10 pertinent studies (13;35–43) published after the search date of our prior meta-analysis (6), increasing the sample size by 40% relative to our previous meta-analysis in adults. Figure 1 shows the PRISMA flow chart (44) of the selected studies. Including the 16 previously included datasets (10–12;45–57) from (6), we retained a total of 26 datasets (10–13;35–43;45–57) for qualitative synthesis and 24 datasets (10–13;35–38;40;41;43;45–57) for meta-analysis [two studies (39;42) did not report coordinates that could be entered into meta-analyses]. The Supplement lists the studies from the updated search that were not included in the meta-analysis, with reasons for their non-inclusion. Table S1 reports the qualitative synthesis of the selected studies. Table S2 summarizes the key findings from each study included in the meta-analysis. Nineteen contrasts “ADHD < controls” and 11 contrasts

“ADHD > controls” were available for the ALE meta-analysis. As the meta-analysis of ADHD-related hyperactivated regions would have been underpowered (24), we did not run it. Excluding two studies (39;42) reporting no significant contrasts between adults with ADHD and controls, we found a total of 12 papers including tasks exploring *inhibition* (10–13;35;40;41;45;47;48;50;52) (reporting, overall, 10 contrasts “Controls > ADHD” and 6 contrasts “ADHD > Controls”), six including *working memory* tasks (37;46;51;54;56;57), six focusing on *attention* tests (40;41;47–50), five assessing *reward processes* (35;36;42;43;49;53), one using the *instructed fear test* (38) and one based on the *paced/unpaced finger tapping test* (55). Therefore, we did not perform planned sub-group analyses based on task type because the number of contrasts was substantially less than 15 (24). Studies with comorbidity-free participants (n=18) (10–13;35–37;39;41;45;46;50;52–57) reported 14 contrasts “Controls > ADHD” and 8 contrasts “ADHD > Controls”. We pooled only the contrasts “Controls > ADHD” from these studies, highlighting the preliminary nature of this analysis, since the number of studies fell just below our threshold. Finally, we could not perform the planned sub-group analysis including only studies with psychostimulant-naïve participants since only 8 papers were available, providing 8 contrasts “Controls > ADHD” and 1 contrast “ADHD > Controls.”

ALE meta-analysis

Table 1 shows ADHD-related hypoactivated brain regions from meta-analysis of the 24 retained studies, across all neuropsychological tasks. Compared to controls, adults with ADHD significantly hypoactivated regions in left putamen, right caudate, left inferior frontal gyrus (pars opercularis) and left temporal pole (Figure 2). When focusing on studies including participants free of comorbidity, only one region (left putamen, MNI coordinates of weighted center: –20, 6, 4) was consistently hypoactivated in adults with ADHD compared to controls.

Functional decoding

Across tasks, the ADHD-related hypoactivated location in left putamen was associated with domains related to cognitive aspects of music (such as music comprehension/production, tone monitor/discrimination), perception/audition and speech/language (Figure S1). Likewise, the second (smaller) ADHD-related hypoactivation in left putamen was again related to cognitive aspects of music and language/speech. The ADHD-related hypoactivated region in left inferior frontal gyrus (pars opercularis), was associated with domains related to action/execution. The ADHD-related hypoactivation in left temporal pole was associated with domains related to cognitive aspects of language and speech. Finally, the ADHD-related hypoactivated region in right caudate was associated with domains related to action/execution, perception/somesthesis, and cognitive aspects of music.

Meta-analytic connectivity modeling (MACM) and clustering

The functional co-activation patterns of each ADHD-related hypoactivated region are displayed in Figure S2. Further details are reported in the Supplement. Clustering the ADHD-related hypoactivated regions supports the interpretation of their co-activation patterns. As shown in Figure 3, based on their meta-analytical co-activation, three regions (left putamen (medial), left temporal pole, and left putamen) clustered closely, a fourth one

was isolated (left inferior frontal gyrus, pars opercularis), and a fifth one (right caudate) was intermediate between the first three and the fourth.

Discussion

This updated meta-analysis of task-based fMRI studies in adults with ADHD is the first to apply meta-analytic connectivity modeling and functional decoding to characterize ADHD-related dysfunctional regions, pointing to possible novel functions of dysfunctional brain regions not necessarily tested in individual studies. These methods leverage a large curated cognitive neuroscience database (BrainMap) to support data-driven interpretation of novel results. This is also the largest ALE meta-analysis of task-based fMRI studies in adults with ADHD, including a number of datasets ($n=24$) that allows a more precise estimation of the effects than a previous ALE meta-analysis (6) of 16 studies. We discuss each ADHD-related hypoactivated region first in relation to previous findings in the ADHD neuroimaging literature and, then consider its functional decoding suggested by the present work. We then provide an overarching interpretation of our results in light of the clustering based on meta-analytic connectivity modeling.

Left putamen

Two ADHD-related hypoactivated regions were located in left putamen. A previous meta-analysis (6) of 39 task-based fMRI studies in children also revealed two large clusters of ADHD-related hypoactivation in putamen. The putamen was also detected as hypoactivated in ADHD in the meta-analysis by Hart et al. when pooling datasets from studies exploring inhibition and attention conducted in children and adults (7). In contrast, a prior meta-analysis of 16 task-based fMRI studies in adults (6) across tasks did not detect significant hypoactivation in this structure. Likewise, significant hypoactivation was not detected in putamen in another (low-powered) meta-analysis of task-based fMRI studies in adults (9). We infer that the increased statistical power of the present meta-analysis allowed us to detect, for the first time, putamen as a hypoactivated region in adults with ADHD, as had been observed in substantially better-powered studies in children with ADHD (6). Indeed, putamen was also implicated in ADHD by a meta-analysis (58) of voxel-based morphometry, which included both pediatric and adult samples. However, the limited number of studies in adults ($n=5$) precluded firm conclusions on structural alterations of the lentiform nucleus in adults with ADHD in that study.

According to the functional decoding based on the activation of the identified regions in more than 7,000 fMRI studies in healthy subjects, the regions in putamen that were hypoactivated in adults with ADHD across studies and tasks in our meta-analysis mapped to tasks mainly related to music comprehension/production and tone monitor/discrimination within the functional domain of cognitive aspects of music. This may seem a surprising result, as alterations in cognitive aspects of music have not been a focus in ADHD research. However, the finding is intriguing and potentially relevant in light of alterations in timing processing that have been proposed as an aspect of the neurocognitive deficits underpinning ADHD, along with other deficits in attention and working memory that are strictly connected to timing functions (59). Indeed, as comprehensively reviewed by Noreika et al.

(60), individuals with ADHD have been found to present multiple deficits in timing functions, including motor timing (estimated with tasks of free tapping, sensorimotor synchronization, and rhythm reproduction), perceptual timing (assessed using tasks of duration discrimination, verbal duration estimation, and duration production and reproduction), and temporal foresight. In the *BrainMap* database, tasks classified in the domain “cognition, music” included, among others, listening to part of a song and then imagining its continuation, discriminating between different music pieces, and performing music. Arguably, all these tasks are strongly related to time and rhythm processing. In fact, putamen is part of a network, including also inferior frontal cortex, supplemental motor area, dorsolateral prefrontal cortex, inferior prefrontal cortex, insula and caudate, that has been meta-analytically identified (61), among others, as involved in perceptual timing, in particular in the range of milliseconds. While most studies on timing alterations have been conducted in children/adolescents (60), our findings suggest that timing/rhythm alterations might be an aspect to consider in the pathophysiology of ADHD in adults as well. However, it is important to appreciate that music processing is underpinned by several functions, including sensorimotor processes, auditory skills, motor skills, auditory memory, working memory, and pitch discrimination. Therefore, our findings should not suggest that rhythm/timing alterations are the only explanation for putamen dysfunction in ADHD. As such, assessing specific training of timing processing, and, possibly, music therapy as intervention strategies for ADHD seems premature. To date, the evidence for the efficacy/effectiveness of music therapy has been scarcely investigated in ADHD (62;63). If confirmed by further empirical studies, our results would also lend support to the proposal that entrainment of neural oscillations be considered as a possible intervention target in ADHD, since individuals with ADHD have been hypothesized to display deficits in entraining intrinsic oscillations to external rhythms (64).

Temporal pole

Another novel finding was ADHD-related hypoactivation of temporal pole, which has not been found in previous meta-analyses of structural or functional MRI studies, in adults or children. However, structural alterations in this region have been reported in previous individual studies in children (65), although an interesting question is whether cortical thinning in the temporal pole persists into adult life (66) or normalizes with age (67). Functional decoding suggested that this specific region may be linked to the domain “cognition/language/semantics.” Indeed, a number of studies found language impairments in children with ADHD, such as deficits in semantic fluency tasks (68), weaknesses in recalling words after delays (69), and deficits in naming speed associated with effortful semantic processing (70). Importantly, such deficits were present even in children with ADHD without comorbid reading disorders, which are also associated with language impairments (71). Semantic deficits have started to be reported in adults with ADHD (72) and our findings provide meta-analytic support to the notion that brain areas involved in semantic processes may persist as dysfunctional in adults with ADHD. Our meta-analysis could not establish to which extent such deficits are related to perceptual, cognitive or specific linguistic subprocesses contributing to semantic deficits. However, previous work supports the notion that temporal pole is involved in retrieval of semantic memory scripts (73). We also note that children with ADHD have been posited to have subtle semantic

processing deficits that affect the speed with which they can access semantic information in relation to deficits in timing mechanisms (70). Therefore, both alteration in music processing and semantic deficits might stem, albeit not exclusively, from dysfunctions in time processing.

Caudate nucleus

The finding of ADHD-related hypoactivation in caudate resonates with previous results from two meta-analyses pooling fMRI studies in children and adults (7;9). The increased power of our meta-analysis allowed us, for the first time, to confirm this finding when pooling a set of studies conducted exclusively in adults. This suggests that putative developmental effects that are usually evoked to explain differences between findings in children and adults might be better accounted for by limited power in previous meta-analyses. Functional decoding related this specific caudate region mainly to the action/execution domain and to the Go/No-Go paradigm, in line with inhibitory deficits that have been classically associated with ADHD (74). Caudate was also related to cognitive aspects of music, possibly reflecting another role of this region in a network underpinning timing processing, as shown in a meta-analysis by Wiener et al. (61).

Inferior frontal gyrus

The fourth ADHD-related hypoactivated location was found in the pars opercularis of inferior frontal gyrus (IFG). This specific area has not been previously reported in meta-analyses of functional or structural MRI studies restricted to adults with ADHD, although it was reported in two meta-analyses combining fMRI studies in children and adults (8;9). Additionally, individual studies found alterations in pars opercularis of IFG both structurally [thinner cortex (75)] and functionally [reduced activation with low memory load and increased activation with high memory load (76)] in children with ADHD. Our results provide novel meta-analytic evidence supporting pars opercularis involvement in the pathophysiology of ADHD in adults. The main functional decoding domains related to IFG, pars opercularis included “action/execution,” which is consistent with well-known executive dysfunction in ADHD (77), as well as “*emotion/fear*.” The latter finding is interesting in light of the recent focus on emotional dysregulation in ADHD (78), although this finding should be considered with caution since it may be driven by the presence of comorbid mood disorders in a portion of individuals in the retained studies.

When limited to studies including only comorbidity-free participants, the only area that was consistently hypoactivated in ADHD was putamen, highlighting the central and specific role of this structure in ADHD. However, this finding should be considered with caution since the number of included contrasts (n=14) is just below the statistically robust range.

As reported above, we did not run the meta-analysis of ADHD-related hyperactivated regions. The only hyperactivation in adults (angular gyrus; middle occipital gyrus) reported by a previous meta-analysis (6) was based on an unpowered meta-analysis (8 contrasts).

Clustering

Clustering of regions reflected their function detected with functional decoding. Indeed, the two regions in putamen and temporal pole clustered together, possibly reflecting that their functions revealed by functional decoding (music-related processes and semantic aspect of language, respectively) are both linked to timing/rhythm processing. The left inferior gyrus, linked to inhibitory executive functions, did not cluster with putamen and temporal pole. Finally, right caudate, which was linked both to executive and music (timing) related tasks, was intermediate between putamen/temporal cluster and left inferior gyrus.

Study Limitations

First, as in previous meta-analyses (6;22), we pooled studies across paradigms to detect consistent aberrations regardless of task type. Our results may have been influenced by the type of included tasks, as a previous meta-analysis (8) probing timing functions (nine studies, but including only one in adults) found significant ADHD-related hypoactivation in the cerebellum that we did not observe. As we still found only one study on timing in adults in our updated meta-analysis, the lack of cerebellar findings likely reflects the current status of task-based fMRI studies in adult ADHD. A wider variety of tasks beyond probes of inhibition and attention thus seems required. Second, the value of using the curated BrainMap database is balanced by its necessarily *a priori* taxonomy, which is admittedly rudimentary. Third, separate meta-analyses could not be performed by ADHD subtype or sex, because separate results for such potentially relevant variables are not typically reported. We note that individual functional MRI studies have reported sex differences in patterns of neuronal activity, for example in tasks of working memory (56), as well as differential activation of regions between the combined and predominantly inattentive subtypes (termed “presentations” in DSM-5), for instance, in go/no-go tasks (79). Fourth, we could not conduct a sub-group meta-analysis including only datasets with psychostimulants-naïve participants. Since there is evidence that psychostimulants have long-term effects on brain function (7–9;80–84), it is not possible to establish to which extent our results were driven by medication effects. Finally, it was not possible to conduct jackknife or reliability analyses.

Conclusions

Besides meta-analytically confirming the role of brain regions involved in executive functions in adults with ADHD, our study adds novel findings to previous smaller meta-analyses of fMRI studies in adults with ADHD, while failing to support previous reports of ADHD-related hyperactivation. In particular, our meta-analysis suggests that dysfunctions in processes underlying music execution/reproduction, as well as semantic processing, might be involved in the pathophysiology of adult ADHD. Since both music execution/reproduction and semantic functions are related to rhythm processing, among other functions, timing deficits deserve further exploration in research on the pathophysiology of adult ADHD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flowchart reporting the search strategy and retrieved studies for the updated search (July 1, 2011–March 15, 2015) of studies in adults with ADHD.

Footnote:

¹ Search terms and results for each database are reported in the Supplement

² Reasons for exclusion are reported in the Supplement

³ Sixteen studies of adults with ADHD were included in Cortese et al. (6)

⁴ Two papers [Morein-Zamir et al., 2014 (39), and Wilbertz et al., 2012 (42)] did not report any significant difference between adults with ADHD and controls in terms of brain regions activated during the planned task.

Figure 2.
Brain regions significantly more activated in controls vs. adults with ADHD in the ALE meta-analysis across tasks.

Figure 3. Clustering of ADHD-related hypoactivated regions based on meta-analytic connectivity modeling.

Table 1

Brain regions exhibiting significantly greater activation in controls relative to adults with ADHD in the meta-analysis across all tasks.

Cluster #	Weighted center ^a			Anatomical label
1	-30	-12	-8	Left putamen (medial)
2	-50	12	6	Left inferior gyrus (pars opercularis)
3	-52	6	-12	Left temporal pole
4	20	16	4	Right caudate
5	-20	6	4	Left putamen

Footnote:

^aMontreal Neurological Institute (MNI) coordinates