

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

Samuele Cortese, F. Xavier Castellanos, Claudia R. Eickhoff, Giulia D'Acunto, Gabriele Masi, Peter T. Fox, Angela R. Laird, and Simon B. Eickhoff

ABSTRACT

BACKGROUND: Task-based functional magnetic resonance imaging (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.

METHODS: We first conducted an activation likelihood estimation meta-analysis of 24 task-based fMRI studies in adults with ADHD. Each ADHD-related dysfunctional region resulting from the activation likelihood estimation meta-analysis was then analyzed using functional decoding based on ~7500 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 coactivation profiles across all the experiments stored in BrainMap (meta-analytic connectivity modeling).

RESULTS: ADHD-related hypoactivation was found in the left putamen, left inferior frontal gyrus (pars opercularis), left temporal pole, and right caudate. Functional decoding mapped the left putamen to cognitive aspects of music perception/reproduction and the left temporal lobe to language semantics; both these regions clustered together on the basis of their meta-analytic functional connectivity. Left inferior gyrus mapped to executive function tasks; right caudate mapped to both executive function 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: Adults, Attention-deficit/hyperactivity disorder, fMRI, Functional decoding, Meta-analysis, Meta-analytic connectivity modeling

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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 magnetic resonance imaging (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,

Cortese *et al.* (6) 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 the right inferior frontal cortex, supplementary motor area, anterior cingulate cortex, and striato-thalamic areas when pooling studies on inhibition, and found ADHD-related hypoactivation in the right dorso-lateral prefrontal cortex, posterior basal ganglia, and thalamic and parietal regions when focusing on attention tasks. In another meta-analysis focused on timing tasks, including studies in both children and adults, Hart *et al.* (8) found ADHD-related hypoactivation in the cerebellar vermis, left inferior prefrontal cortex and insula, and 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 the 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 the right insula, right caudate, and right lentiform nucleus and significantly increased activation in the right inferior occipital gyrus, right precuneus, and right superior parietal lobule.

Given the number of studies published in the intervening 4 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. MACM (19) is another data-driven method to assess the functional coactivation between a particular region of interest and all other voxels in the brain. Regions with similar coactivation 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 coactivation patterns of each ADHD-related hypo- or hyperactivated region resulting from the updated meta-analysis; and 4) clustered ADHD-related hypo- or hyperactivated regions, on the basis of their coactivation patterns, to identify possible dysfunctional subnetworks 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 subgroup 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 (III, IV, IV-TR) or ICD (9 or 10); 3) a matched group of healthy subjects was included; 4) data were reported as three-dimensional 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 washout; 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, because these may represent a neurobiologically distinct entity.

Planned Meta-Analyses

As in previous studies (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 in which participants did not have comorbid psychiatric disorders. Finally, we planned a subgroup analysis including only studies with stimulant-naïve participants. When exploring the feasibility of such subgroup 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 Montreal Neurological Institute coordinates using the *icbm2tal* (Lancaster) transformation (25). Afterward, ALE was used to identify areas showing a convergence of coordinates across experiments. We used random-effects inference. Taking the union across modeled activation maps yielded voxelwise 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 $p < .05$). All analyses were run using in-house MATLAB (The MathWorks, Inc., Natick, MA) 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 labeling. Studies are coded in terms of behavioral domain and paradigm class. Behavioral domains

(30) include the main categories of cognition, action, perception, emotion, and interoception, as well as their related subcategories (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/subscribe/> 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 7500 task-based experiments at time of analysis (16). To avoid preselection 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](#).

MACM and Clustering

The functional coactivation 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 coactivated 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 coactivation patterns of meta-analytically derived regions. We applied multidimensional scaling 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 (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flow chart (44) of the selected studies. Including the 16 previously included datasets (10–12,45–57) from Cortese *et al.* (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 noninclusion. [Supplemental Table S1](#) reports the qualitative synthesis of the selected studies. [Supplemental Table S2](#) summarizes the key findings from each study included in the meta-analysis. Nineteen contrasts of ADHD < controls and 11 contrasts of 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 of controls > ADHD and six contrasts of 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 (35,36,43,49,53), one using the instructed fear test (38), and one based on the paced or unpaced finger tapping test (55). Therefore, we did not perform planned subgroup analyses on the basis of 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 of controls > ADHD and eight contrasts of ADHD > controls. We pooled only the contrasts of controls > ADHD from these studies, highlighting the preliminary nature of this analysis, because the number of studies fell just below our threshold. Finally, we could not perform the planned subgroup analysis including only studies with psychostimulant-naïve participants because only eight papers were available, providing eight contrasts of controls > ADHD and one contrast of 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 the left putamen, right caudate, left inferior frontal gyrus (IFG) (pars opercularis), and left temporal pole ([Figure 2](#)). When focusing on studies including participants free of comorbidity, only one region (left putamen, Montreal Neurological Institute 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 the left putamen was associated with domains related to cognitive aspects of music (e.g., music comprehension and production, tone monitor and discrimination), perception and audition, and speech and language ([Supplemental Figure S1](#)). Likewise, the second (smaller) ADHD-related hypoactivation in the left putamen was again related to cognitive aspects of music as well as language and speech. The ADHD-related hypoactivated region in the left IFG (pars opercularis) was associated with domains related to action or execution. The ADHD-related hypoactivation in the left temporal pole was associated with domains related to cognitive aspects of language and speech. Finally, the ADHD-related hypoactivated region in the right caudate was associated with domains related to action and execution, perception and somesthesia, and cognitive aspects of music.

MACM and Clustering

The functional coactivation patterns of each ADHD-related hypoactivated region are displayed in [Supplemental Figure S2](#). Further details are reported in the [Supplement](#). Clustering the

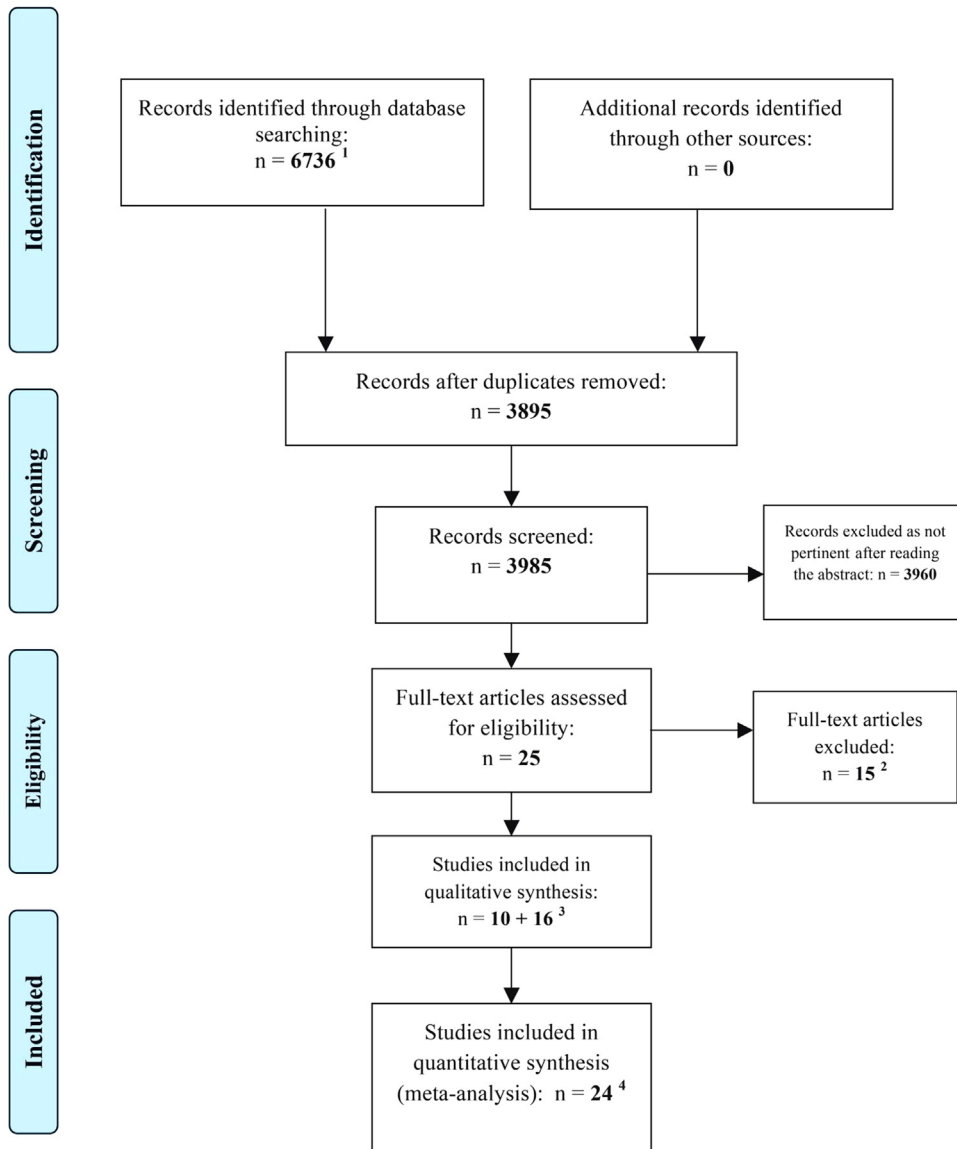


Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flow-chart reporting the search strategy and retrieved studies for the updated search (July 1, 2011, to March 15, 2015) of studies in adults with attention-deficit/hyperactivity disorder (ADHD). ¹Search terms and results for each database are reported in the Supplement. ²Reasons for exclusion are reported in the Supplement. ³Sixteen studies of adults with ADHD were included in Cortese *et al.* (6). ⁴Two papers [Morein-Zamir *et al.* (39) and Wilbertz *et al.* (42)] did not report any significant difference between adults with ADHD and controls in terms of brain regions activated during the planned task.

ADHD-related hypoactivated regions supports the interpretation of their coactivation patterns. As shown in Figure 3, on the basis of their meta-analytical coactivation, three regions (left putamen [medial], left temporal pole, and left putamen) clustered closely, a fourth one was isolated (left IFG, pars

opercularis), and a fifth one (right caudate) was intermediate between the first three and the fourth.

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

^aMontreal Neurological Institute coordinates.

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 large number of datasets ($n = 24$) that allow a more precise estimation of the effects than a previous ALE meta-analysis (6) of 16 studies. We discuss each ADHD-

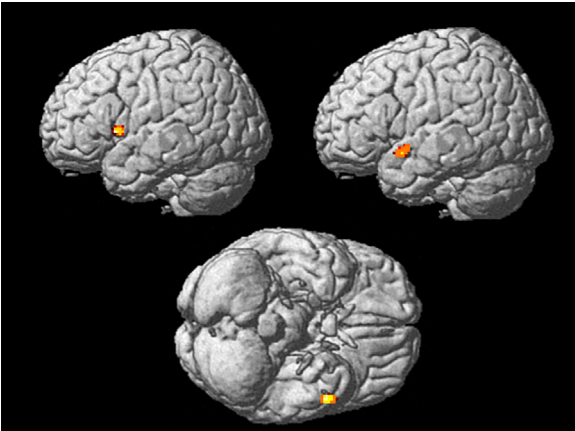


Figure 2. Brain regions significantly more activated in controls vs. adults with attention-deficit/hyperactivity disorder in the activation likelihood estimation meta-analysis across tasks.

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 on the basis of meta-analytic connectivity modeling.

Left Putamen

Two ADHD-related hypoactivated regions were located in the 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 the putamen. The putamen was also detected as hypoactivated in ADHD in the meta-analysis by Hart *et al.* (7) when pooling datasets from studies exploring inhibition and attention conducted in children and adults. 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 the putamen in another (low-powered) meta-analysis of task-based fMRI

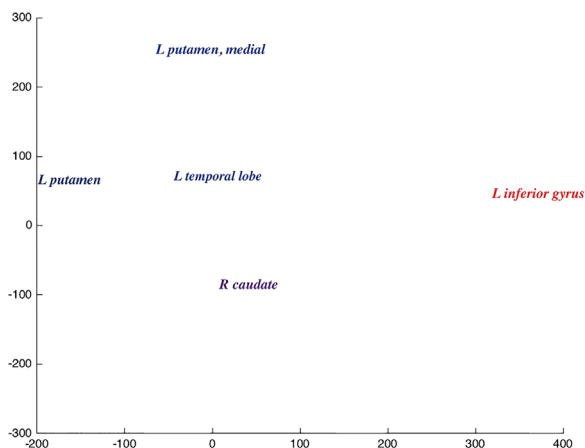


Figure 3. Clustering of attention-deficit/hyperactivity disorder-related hypoactivated regions on the basis of meta-analytic connectivity modeling.

studies in adults (9). We infer that the increased statistical power of the present meta-analysis allowed us to detect, for the first time, the putamen as a hypoactivated region in adults with ADHD, as had been observed in substantially better-powered studies in children with ADHD (6). Indeed, the 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 7000 fMRI studies in healthy subjects, the regions in the 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, the putamen is part of a network, including also the inferior frontal cortex, supplementary 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. Although most studies on timing alterations have been conducted in children and adolescents (60), our findings suggest that timing and 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 and 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 and 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, because 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 fMRI 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 of cognition, language, and 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 and 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 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 the 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 the IFG pars opercularis included action and execution, which is consistent with well-known executive dysfunction in ADHD (77), as well as emotion and 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 because 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 the putamen, highlighting the central and specific role of this structure in ADHD. However, this finding should be considered with caution because the number of included contrasts ($n = 14$) is just below the statistically robust range.

As reported previously, 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 (eight contrasts).

Clustering

Clustering of regions reflected their function detected with functional decoding. Indeed, the two regions in the 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 linked to both timing and rhythm processing. The left inferior gyrus, linked to inhibitory executive functions, did not cluster with the putamen and temporal pole. Finally, the right caudate, which was linked to both executive and music (timing)-related tasks, was intermediate between the putamen and 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 fMRI 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 subgroup meta-analysis including only datasets with psychostimulant-naïve participants. Because 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 and reproduction, as well as semantic processing, might be involved in the pathophysiology of adult ADHD. Because both music execution and 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.

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ARTICLE INFORMATION

From the Academic Unit of Psychology (SC), Developmental Brain-Behaviour Laboratory, and Clinical and Experimental Sciences (CNS and Psychiatry) (SC), Faculty of Medicine, University of Southampton, Southampton, United Kingdom; The Child Study Center (SC, FXC), Hassenfeld Children’s Hospital of New York, NYU Langone Medical Center, New York; Nathan S. Kline Institute for Psychiatric Research (FXC), Orangeburg, New York; Research Imaging Institute (PTF) and Department of Radiology (PTF), University of Texas Health Science Center; and South Texas Veterans Health Care System (PTF), San Antonio, Texas; Department of Physics (ARL), Florida International University, Miami, Florida; IRCCS Stella Maris (SC, GD, GM), Scientific Institute of Child Neurology and Psychiatry, Calambrone, Italy; Institute of Neuroscience and Medicine (INM-1) (CRE, SBE), Research Center Jülich GmbH, Jülich; Department of Psychiatry (CRE), Psychotherapy and Psychosomatics, RWTH Aachen University, Aachen; and the Institute of Clinical Neuroscience and Medical Psychology (SBE), Heinrich Heine University Duesseldorf, Duesseldorf, Germany.

Address correspondence to Samuele Cortese, M.D., Ph.D., Academic Unit of Psychology, Developmental Brain-Behaviour Laboratory, University of Southampton, Southampton, United Kingdom; E-mail: samuele.cortese@gmail.com.

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