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ATTENTION-DEFICIT DISORDER (R BUSSING, SECTION EDITOR)

Neuroimaging of Attention-Deficit/Hyperactivity Disorder: Current Neuroscience-Informed Perspectives for Clinicians

Samuele Cortese · F. Xavier Castellanos

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Abstract The neuroimaging literature on attention-deficit/hyperactivity disorder (ADHD) is growing rapidly. Here, we provide a critical overview of neuroimaging studies published recently, highlighting perspectives that may be of relevance for clinicians. After a comprehensive search of PubMed, Ovid, Web of Science, and EMBASE, we located 41 pertinent papers published between January 2011 and April 2012, comprising both structural and functional neuroimaging studies. This literature is increasingly contributing to the notion that the pathophysiology of ADHD reflects abnormal interplay among large-scale brain circuits. Moreover, recent studies have begun to reveal the mechanisms of action of pharmacological treatment. Finally, imaging studies with a developmental perspective are revealing the brain correlates of ADHD over the lifespan, complementing clinical observations on the phenotypic continuity and discontinuity of the disorder. However, despite the increasing potential to eventually inform clinical practice, current imaging studies do not have validated applications in day-to-day clinical practice. Although novel analytical techniques are likely to accelerate the pace of translational applications, at the present we advise caution regarding inappropriate commercial misuse of imaging techniques in ADHD.

Keywords Attention-deficit/hyperactivity disorder · ADHD · Neuroscience · Neuroimaging · MRI · Treatment · Pathophysiologic mechanisms · Emotional reactivity · Emotional processing

S. Cortese (✉) · F. X. Castellanos
Phyllis Green and Randolph Cowen Institute for Pediatric Neuroscience, Child Study Center of the NYU Langone Medical Center,
One Park Avenue, 8th Floor,
New York, NY 10016, USA
e-mail: samuele.cortese@gmail.com

S. Cortese
Child Neuropsychiatry Unit, G. B. Rossi Hospital,
Department of Life Science and Reproduction, Verona University,
Verona, Italy

S. Cortese
UMR_S INSERM U 930, ERL 3106, François-Rabelais University, Child Psychiatry Centre, University Hospital,
Tours, France

F. X. Castellanos
Nathan S. Kline Institute for Psychiatric Research,
Orangeburg, NY, USA

Introduction

The neuroimaging literature on attention-deficit/hyperactivity disorder (ADHD) is growing rapidly. For example, a Pubmed search of "ADHD AND imaging" in 2001 retrieved 26 references, 81 in 2005, and 141 in 2010. This growth has been accompanied by:

1. a shift in the neurobiological conceptualization of ADHD from a primarily fronto-striatal disorder to a condition characterized by abnormal interplay among several structurally and functionally defined brain networks;
2. the introduction of new neuroimaging techniques; and
3. the use of increasingly sophisticated analytical approaches.

Clinicians may find it challenging to stay abreast of this growing and complex literature. Here, we provide an overview of salient trends in the neuroimaging research on ADHD published recently (from January 2011 to April 2012), highlighting the emergence of themes and perspectives that are, or may become, relevant to

clinical practice. We present key findings from two main types of neuroimaging study:

1. structural, including voxel-based morphometry (VBM), cortical thickness, and diffusion tensor imaging (DTI) measures; and
2. functional, whether task-based functional MRI (fMRI), resting state MRI (R-fMRI), near-infrared spectroscopy, positron emission tomography (PET), or single-photon emission computed tomography (SPECT).

We also review recent neuroimaging studies conducted to elucidate the mechanism of action and/or effectiveness of ADHD treatments.

Methods

Study Search

Although not strictly speaking a systematic review, because we did not conduct a detailed appraisal of the quality of the reviewed studies, we performed a comprehensive search across a broad set of databases using a large number of search terms to minimize the chance of missing relevant studies. We searched PubMed, Ovid (including PsycINFO and Ovid MEDLINE), Web of Science (SCI-EXPANDED, SSCI, A&HCI), and EMBASE from 01.01.2011 to 04.14.2012. The search terms, adapted for each database, are reported in Table 1.

Inclusion and Exclusion Criteria

We included empirical studies using any neuroimaging technique. Only studies in which the diagnosis of ADHD was performed according to standard criteria (DSM-IV or ICD-10) were retained. Studies that included only individuals with ADHD plus specific comorbidities (e.g., ADHD +bipolar disorder) were excluded as were abstracts of conference presentations. Given the hard-won recognition by the field of the importance of correction for multiple comparisons in neuroimaging analysis, we excluded studies that did not correct for multiple comparisons or in which the use of correction methods was unclear. Finally, we excluded fMRI studies with sample sizes <15 per group, because underpowered studies are most likely to report type I errors [1].

Results

Figure 1 shows the search results according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart [2]. A total of 41 [3–9, 10••, 11•, 12, 13•, 14, 15, 16••, 17•, 18, 19•, 20••, 21, 22••, 23, 24, 25•, 26••, 27–29, 30••, 31–35, 36••, 37, 38, 39••, 40••, 41••, 42••, 43] studies were retained; these are discussed below. Table 2 reports excluded studies.

Discussion

Structural Imaging

Most of the early structural MRI studies in ADHD contrasted individuals with ADHD and comparisons to identify ADHD-related differences. This large body of research was summarized recently in two meta-analyses [16••, 26••] with complementary methods applied to largely overlapping studies and converging results. Pooling 14 VBM datasets including 378 individuals with ADHD and 344 comparisons, Nakao et al. [26••] found a significant reduction of gray matter volume in the right basal ganglia (putamen, globus pallidus, and caudate), in agreement with fronto-striatal models of ADHD pathophysiology. Interestingly, estimates of right putamen gray matter volume increased with age, suggesting that ADHD patients partially "outgrow" basal ganglia deficits. Reduced right globus pallidus and putamen volumes were also found by Frodl et al. [16••] in a meta-analysis of 11 VBM studies, encompassing 320 individuals with ADHD and 288 comparisons (all of which were included in Nakao et al. [26••]). The two meta-analyses also addressed an issue of concern to patients and clinicians, i.e., the possible effect of ADHD drugs on brain structure. Both Nakao et al. [26••] and Frodl et al. [16••] provide suggestive VBM evidence that stimulants are associated with reduction or even normalization of structural abnormalities in ADHD. Frodl et al. [16••] also examined eight studies in which caudate volumes were hand-traced and found significant evidence for reduced volumetric reductions in bilateral caudate in studies with a higher proportion of stimulant-treated subjects [16••].

Concern regarding disentangling correlates of the diagnosis from possible consequences of medication treatment has increasingly motivated participant selection. In a study of 31 adults with ADHD and 31 comparisons in which only one patient had ever been treated with stimulants and all participants were medication-free for at least 6 months, Ahrendts et al. [3] found significant gray matter volume reduction in bilateral visual cortex only. The authors interpreted these unexpected occipital findings as expression of impairments in early-stage "subexecutive" attentional mechanisms. Similarly, Almeida Montes et al. [4], focusing on cerebellar morphometry in females, included only stimulant-naïve children, adolescents, and adults, concluding that cerebellar volumetric reductions are not ascribable

Table 1 Specific search terms for each database

PUBMED (MEDLINE): (ADHD OR attention deficit hyperactivity disorder OR attention-deficit/hyperactivity disorder OR attention deficit disorder with hyperactivity OR hyperkinetic syndrome OR syndrome hyperkinetic OR hyperactivity disorder OR hyperactive child syndrome OR childhood hyperkinetic syndrome OR attention deficit disorder OR deficit disorder attention OR disorder attention deficit OR addh OR overactive child syndrome OR attention deficit hyperkinetic disorder OR hyperkinetic disorder OR attention deficit disorder hyperactivity OR child attention deficit disorder OR hyperkinetic syndrome childhood OR hyperkinesis) AND (Imaging OR neuroimaging OR magnetic resonance imaging OR MRI OR nuclear magnetic resonance imaging OR NMR imaging OR functional imaging OR functional magnetic imaging OR Functional MRI OR fMRI OR Positron emission tomography OR PET OR Tomography Positron-Emission OR positron emission tomographic scan OR positron tomography OR Positron emission tomography computer assisted OR Computer assisted positron emission tomography OR Positron emission computed tomography OR Single Photon Emission Compute Tomography OR CT Scan Single-Photon Emission OR Emission-Computed Tomography Single-Photon OR Tomography Single-Photon Emission-Computed OR SPECT OR computer assisted tomography single photon emission OR emission computer tomography single photon OR tomography emission-computed single-photon)

PsycInfo*:* (ADHD OR attention deficit hyperactivity disorder OR attention deficit disorder with hyperactivity OR hyperkinetic syndrome OR syndrome hyperkinetic OR hyperactivity disorder OR hyperactive child syndrome OR childhood hyperkinetic syndrome OR attention deficit disorder OR deficit disorder attention OR disorder attention deficit OR addh OR overactive child syndrome OR attention deficit hyperkinetic disorder OR hyperkinetic disorder OR attention deficit disorder hyperactivity OR child attention deficit disorder OR hyperkinetic syndrome childhood OR hyperkinesis OR Attention deficit disorder / OR ((attenti$) adj3 (deficit$ OR disorder$ or hyperactiv$ OR hyper?activ$ OR adhd OR addh OR ad??hd)) OR ((hyperkin$ OR hyper?kin$) adj3 (deficit$ OR disorder$ OR hkd))) AND (Imaging OR neuroimaging OR magnetic resonance imaging OR MRI OR nuclear magnetic resonance imaging OR NMR imaging OR functional imaging OR functional magnetic imaging OR Functional MRI OR fMRI OR Positron emission tomography OR PET OR Tomography Positron-Emission OR positron emission tomographic scan OR positron tomography OR Positron emission tomography computer assisted OR Computer assisted positron emission tomography OR Positron emission computed tomography OR Single Photon Emission Compute Tomography OR CT Scan Single-Photon Emission OR Emission-Computed Tomography Single-Photon OR Tomography Single-Photon Emission-Computed OR SPECT OR computer assisted tomography single photon emission OR emission computer tomography single photon OR tomography emission-computed single-photon)

Ovid Medline: (ADHD OR attention deficit hyperactivity disorder OR attention deficit disorder with hyperactivity OR hyperkinetic syndrome OR syndrome hyperkinetic OR hyperactivity disorder OR hyperactive child syndrome OR childhood hyperkinetic syndrome OR attention deficit disorder OR deficit disorder attention OR disorder attention deficit OR addh OR overactive child syndrome OR attention deficit hyperkinetic disorder OR hyperkinetic disorder OR attention deficit disorder hyperactivity OR child attention deficit disorder OR hyperkinetic syndrome childhood OR hyperkinesis OR Attention deficit disorder / OR ((attenti$) adj3 (deficit$ OR disorder$ or hyperactiv$ OR hyper?activ$ OR adhd OR addh OR ad??hd)) OR ((hyperkin$ OR hyper?kin$) adj3 (deficit$ OR disorder$ OR hkd))) AND (Imaging OR neuroimaging OR magnetic resonance imaging OR MRI OR nuclear magnetic resonance imaging OR NMR imaging OR functional imaging OR functional magnetic imaging OR Functional MRI OR fMRI OR Positron emission tomography OR PET OR Tomography Positron-Emission OR positron emission tomographic scan OR positron tomography OR Positron emission tomography computer assisted OR Computer assisted positron emission tomography OR Positron emission computed tomography OR Single Photon Emission Compute Tomography OR CT Scan Single-Photon Emission OR Emission-Computed Tomography Single-Photon OR Tomography Single-Photon Emission-Computed OR SPECT OR computer assisted tomography single photon emission OR emission computer tomography single photon OR tomography emission-computed single-photon)

EMBASE + EMBASE CLASSIC: (ADHD OR attention deficit hyperactivity disorder OR attention deficit disorder with hyperactivity OR hyperkinetic syndrome OR syndrome hyperkinetic OR hyperactivity disorder OR hyperactive child syndrome OR childhood hyperkinetic syndrome OR attention deficit disorder OR deficit disorder attention OR disorder attention deficit OR addh OR overactive child syndrome OR attention deficit hyperkinetic disorder OR hyperkinetic disorder OR attention deficit disorder hyperactivity OR child attention deficit disorder OR hyperkinetic syndrome childhood OR hyperkinesis OR Attention deficit disorder / OR ((attenti$) adj3 (deficit$ OR disorder$ or hyperactiv$ OR hyper?activ$ OR adhd OR addh OR ad??hd)) OR ((hyperkin$ OR hyper?kin$) adj3 (deficit$ OR disorder$ OR hkd))) AND (Imaging OR neuroimaging OR magnetic resonance imaging OR MRI OR nuclear magnetic resonance imaging OR NMR imaging OR functional imaging OR functional magnetic imaging OR Functional MRI OR fMRI OR Positron emission tomography OR PET OR Tomography Positron-Emission OR positron emission tomographic scan OR positron tomography OR Positron emission tomography computer assisted OR Computer assisted positron emission tomography OR Positron emission computed tomography OR Single Photon Emission Compute Tomography OR CT Scan Single-Photon Emission OR Emission-Computed Tomography Single-Photon OR Tomography Single-Photon Emission-Computed OR SPECT OR computer assisted tomography single photon emission OR emission computer tomography single photon OR tomography emission-computed single-photon)

WEB OF KNOWLEDGE **(Web of science (science citation index expanded), Biological abstracts, Biosis, Food science and technology abstracts):** (ADHD OR attention deficit hyperactivity disorder OR attention deficit disorder with hyperactivity OR hyperkinetic syndrome OR syndrome hyperkinetic OR hyperactivity disorder OR hyperactive child syndrome OR childhood hyperkinetic syndrome OR attention deficit disorder OR deficit disorder attention OR disorder attention deficit OR addh OR overactive child syndrome OR attention deficit hyperkinetic disorder OR hyperkinetic disorder OR attention deficit disorder hyperactivity OR child attention deficit disorder OR hyperkinetic syndrome childhood OR hyperkinesis) AND (Imaging OR neuroimaging OR magnetic resonance imaging OR MRI OR nuclear magnetic resonance imaging OR NMR imaging OR functional imaging OR functional magnetic imaging OR Functional MRI OR fMRI OR Positron emission tomography OR PET OR Tomography Positron-Emission OR positron emission tomographic scan OR positron tomography OR Positron emission tomography computer assisted OR Computer assisted positron emission tomography OR Positron emission computed tomography OR Single Photon Emission Compute Tomography OR CT Scan Single-Photon Emission OR Emission-Computed Tomography Single-Photon OR Tomography Single-Photon Emission-Computed OR SPECT OR computer assisted tomography single photon emission OR emission computer tomography single photon OR tomography emission-computed single-photon)

Table 1 (continued)

ERIC: (ADHD OR attention deficit hyperactivity disorder OR attention deficit disorder with hyperactivity OR hyperkinetic syndrome OR syndrome hyperkinetic OR hyperactivity disorder OR hyperactive child syndrome OR childhood hyperkinetic syndrome OR attention deficit disorder OR deficit disorder attention OR disorder attention deficit OR addh OR overactive child syndrome OR attention deficit hyperkinetic disorder OR hyperkinetic disorder OR attention deficit disorder hyperactivity OR child attention deficit disorder OR hyperkinetic syndrome childhood OR hyperkinesis) AND (Imaging OR neuroimaging OR magnetic resonance imaging OR MRI OR nuclear magnetic resonance imaging OR NMR imaging OR functional imaging OR functional magnetic imaging OR Functional MRI OR fMRI OR Positron emission tomography OR PET OR Tomography Positron-Emission OR positron emission tomographic scan OR positron tomography OR Positron emission tomography computer assisted OR Computer assisted positron emission tomography OR Positron emission computed tomography OR Single Photon Emission Compute Tomography OR CT Scan Single-Photon Emission OR Emission-Computed Tomography Single-Photon OR Tomography Single-Photon Emission-Computed OR SPECT OR computer assisted tomography single photon emission OR emission computer tomography single photon OR tomography emission-computed single-photon)

CINAHAL PLUS: (ADHD OR attention deficit hyperactivity disorder OR attention deficit disorder with hyperactivity OR hyperkinetic syndrome OR syndrome hyperkinetic OR hyperactivity disorder OR hyperactive child syndrome OR childhood hyperkinetic syndrome OR attention deficit disorder OR deficit disorder attention OR disorder attention deficit OR addh OR overactive child syndrome OR attention deficit hyperkinetic disorder OR hyperkinetic disorder OR attention deficit disorder hyperactivity OR child attention deficit disorder OR hyperkinetic syndrome childhood OR hyperkinesis) AND (Imaging OR neuroimaging OR magnetic resonance imaging OR MRI OR nuclear magnetic resonance imaging OR NMR imaging OR functional imaging OR functional magnetic imaging OR Functional MRI OR fMRI OR Positron emission tomography OR PET OR Tomography Positron-Emission OR positron emission tomographic scan OR positron tomography OR Positron emission tomography computer assisted OR Computer assisted positron emission tomography OR Positron emission computed tomography OR Single Photon Emission Compute Tomography OR CT Scan Single-Photon Emission OR Emission-Computed Tomography Single-Photon OR Tomography Single-Photon Emission-Computed OR SPECT OR computer assisted tomography single photon emission OR emission computer tomography single photon OR tomography emission-computed single-photon

to stimulant treatment. Other recent studies have continued to confirm the notion that ADHD is characterized by structural abnormalities in fronto-striatal [6, 24, 35] and cerebellar regions [4, 7].

Another recent trend in structural studies has been a focus on cortical thickness, which defines gray matter regions with high spatial resolution [30••]. Contrary to other reports on ADHD, Duerden et al. [15] found significantly increased cortical thickness in primary sensorimotor cortex in 13 adults with ADHD vs. 20 comparisons. These effects were largely accounted for by loss of age-related decreases in cortical thickness in ADHD, which supported the speculation that they reflect maturational abnormalities. Another cross-sectional study in medication-naïve children, adolescents, and adults reported significantly reduced cortical thickness in ADHD vs. comparisons predominantly in frontoparietal regions, and increased cortical thickness primarily in occipital regions, in all age groups [5].

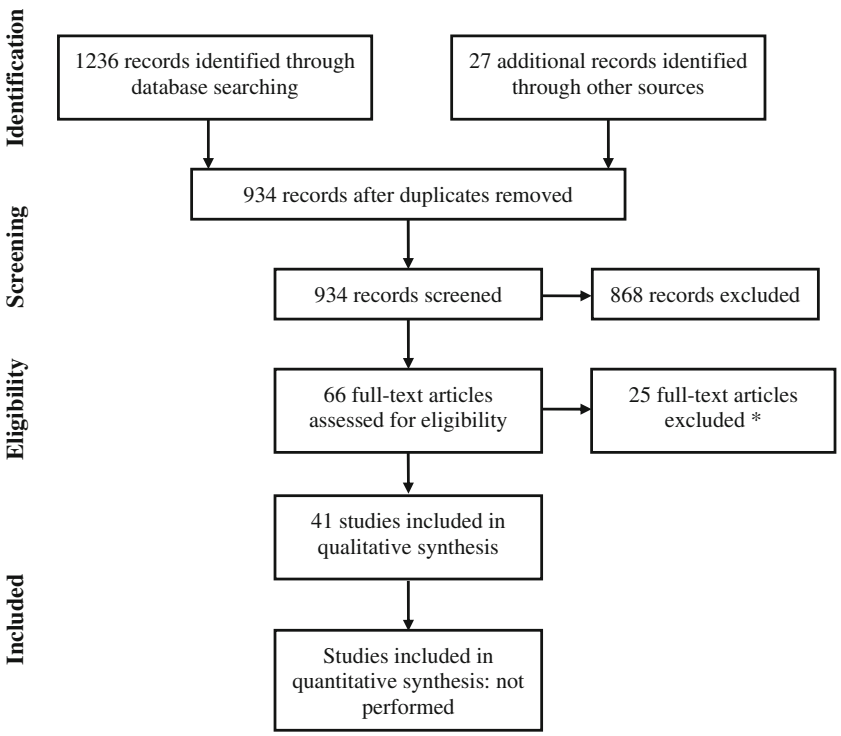

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of retained studies. *Nineteen studies (Table 2 [1–9, 10••, 11•, 12, 13•, 14, 15, 16••, 17•, 18, 19•]) were excluded because of sample size <15 (in at least one study subgroup). One study (Table 2, Ref. [20••]) was discarded because results were based on analyses uncorrected for multiple comparisons. Two studies (Table 2, Refs. [21, 22••]) assessing individuals with self-reported ADHD symptoms, without a formal interview, were excluded. One was not an original empirical study (Table 2, Ref. [23]). Finally, we did not include two studies that examined, respectively, individuals with ADHD plus bipolar disorder (Table 2, Ref. [24]) and ADHD plus developmental coordination disorder (Table 2, Ref. [25•])

Table 2 Studies not retained in the review

1 Braet W, Johnson KA, Tobin CT, Acheson R, McDonnell C, Hawi Z, Barry E, Mulligan A, Gill M, Bellgrove MA, Robertson IH, Garavan H. fMRI activation during response inhibition and error processing: The role of the DAT1 gene in typically developing adolescents and those diagnosed with ADHD. Neuropsychologia 2011; 49: 1641-50.

2 Brown AB, Biederman J, Valera E, Makris N, Doyle A, Whitfield-Gabrieli S, Mick E, Spencer T, Faraone S, Seidman L. Relationship of DAT1 and adult ADHD to task-positive and task-negative working memory networks. Psychiatry Res 2011;193:7-16.

3 Cannon RC, Kerson C, Hampshire A. sLORETA and fMRI detection of medial prefrontal default network anomalies in adult ADHD; J Neurother 2011;15: 358-373.

4 Cubillo A, Halari R, Giampietro V, Taylor E, Rubia K. Fronto-striatal underactivation during interference inhibition and attention allocation in grown up children with attention deficit/hyperactivity disorder and persistent symptoms. Psychiatry Res 2011;193:17-27.

5 Cubillo A, Halari R, Smith A, Taylor E, Rubia K. A review of fronto-striatal and fronto-cortical brain abnormalities in children and adults with Attention Deficit Hyperactivity Disorder (ADHD) and new evidence for dysfunction in adults with ADHD during motivation and attention. Cortex 2012;48:194-215.

6 Fassbender C, Schweitzer JB, Cortes CR, Tagamets MA, Windsor TA, Reeves GM, Gullapalli R. Working memory in attention deficit/hyperactivity disorder is characterized by a lack of specialization of brain function. PLoS One 2011;6:e27240.

7 Hoogman M, Aarts E, Zwiers M, Slaats-Willemse D, Naber M, Onnink M, Cools R, Kan C, Buitelaar J, Franke B. Nitric oxide synthase genotype modulation of impulsivity and ventral striatal activity in adult ADHD patients and healthy comparison subjects. Am J Psychiatry 2011;168:1099-1106.

8 Lemiere J, Danckaerts M, Van HW, Mehta MA, Peeters R, Sunaert S, Sonuga-Barke E. Brain activation to cues predicting inescapable delay in adolescent Attention Deficit/Hyperactivity Disorder: an fMRI pilot study. Brain Res 2012;1450:57-66.

9 Malisza KL, Clancy C, Shiloff D, Holden J, Jones C, Paulson K, Yu DC, Summers R, Chudley AE. Functional magnetic resonance imaging of facial information processing in children with autistic disorder, attention deficit hyperactivity disorder and typically developing controls. Int J Adolesc Med Health 2011;23:269-277.

10 Mulder MJ, van BJ, van EH, Durston S: Functional connectivity between cognitive control regions is sensitive to familial risk for ADHD. Hum Brain Mapp 2011;32:1511-1518.

11 Mulligan RC, Knopik VS, Sweet LH, Fischer M, Seidenberg M, Rao SM. Neural correlates of inhibitory control in adult attention deficit/hyperactivity disorder: evidence from the Milwaukee longitudinal sample. Psychiatry Res 2011;194:119-129.

12 Prehn-Kristensen A, Krauel K, Hinrichs H, Fischer J, Malecki U, Schuetze H, Wolff S, Jansen O, Duezel E, Baving L. Methylphenidate does not improve interference control during a working memory task in young patients with attention-deficit hyperactivity disorder. Brain Res 2011; 1388: 56-68.

13 Rubia K, Halari R, Cubillo A, Smith AB, Mohammad AM, Brammer M, Taylor E. Methylphenidate Normalizes Fronto-Striatal Underactivation During Interference Inhibition in Medication-Naive Boys with Attention-Deficit Hyperactivity Disorder. Neuropsychopharmacology 2011; 36: 1575-86.

14 Rubia K, Cubillo A, Woolley J, Brammer MJ, Smith A. Disorder-specific dysfunctions in patients with attention-deficit/hyperactivity disorder compared to patients with obsessive-compulsive disorder during interference inhibition and attention allocation. Hum Brain Mapp 2011;32:601-611.

15 Rubia K, Halari R, Mohammad AM, Taylor E, Brammer M. Methylphenidate normalizes frontocingulate underactivation during error processing in attention-deficit/hyperactivity disorder. Biol Psychiatry 2011;70:255-262.

16 Schlochtermeier L, Stoy M, Schlagenhauf F, Wrase J, Park SQ, Friedel E, Huss M, Lehmkuhl U, Heinz A, Strohle A. Childhood methylphenidate treatment of ADHD and response to affective stimuli. Eur Neuropsychopharmacol 2011;21:646-654.

17 Siniatchkin M, Glatthaar N, von Muller GG, Prehn-Kristensen A, Wolff S, Knochel S, Steinmann E, Sotnikova A, Stephani U, Petermann F, Gerber WD. Behavioural treatment increases activity in the cognitive neuronal networks in children with attention deficit/hyperactivity disorder. Brain Topogr 2012;25:332-344.

18 Spinelli S, Joel S, Nelson TE, Vasa RA, Pekar JJ, Mostofsky SH. Different neural patterns are associated with trials preceding inhibitory errors in children with and without attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2011;50:705-715.

19 Spinelli S, Vasa RA, Joel S, Nelson TE, Pekar JJ, Mostofsky SH. Variability in post-error behavioral adjustment is associated with functional abnormalities in the temporal cortex in children with ADHD. J Child Psychol Psychiatry 2011;52:808-816.

20 Kim JH, Chung YI, Lee JS, Kim IJ, Kim YK, Kim SJ. Voxel-based statistical analysis of regional cerebral glucose metabolism in children with attention-deficit hyperactivity disorder. Neur Reg Res 2011; 36: 2850-2855.

21 Hoogman M, Rijpkema M, Janss L, Brunner H, Fernandez G, Buitelaar J, Franke B, Arias-Vasquez A. Current self-reported symptoms of attention deficit/hyperactivity disorder are associated with total brain volume in healthy adults. PLoS One 2012;7:e31273.

22 Stark R, Bauer E, Merz CJ, Zimmermann M, Reuter M, Plichta MM, Kirsch P, Lesch KP, Fallgatter AJ, Vaitl D, Herrmann MJ. ADHD related behaviors are associated with brain activation in the reward system. Neuropsychologia 2011;49:426-434.

23 Di Tommaso MC. A comparative study of bipolar disorder and attention deficit hyperactivity disorder through the measurement of regional cerebral blood flow. J Biol Regul Homeost Agents 2012;26:1-6.

24 Brown A, Biederman J, Valera E, Lomedico A, Aleardi M, Makris N, Seidman LJ. Working memory network alterations and associated symptoms in adults with ADHD and Bipolar Disorder. J Psychiatr Res 2012;46:476-483.

25 Yeh CB, Huang WS, Lo MC, Chang CJ, Ma KH, Shyu JF. The rCBF brain mapping in adolescent ADHD comorbid developmental coordination disorder and its changes after MPH challenging. Eur J Paediatr Neurol 2012, in press.

A limitation of studies of adults with ADHD has been reliance on retrospective reports of childhood symptoms for diagnosis of ADHD, which may be problematic [45]. This was bypassed in a study assessing cortical thickness and VBM at 33-year follow-up for 59 adults with ADHD established in childhood (probands) and 80 comparisons free of ADHD in childhood [30••]. Proal et al. [30••] found significantly thinner cortex in ADHD probands than in comparisons in the dorsal attentional network and limbic areas

[30••]. Subcortically, gray matter volume was significantly reduced in ADHD probands vs. comparisons in the right caudate, right thalamus, and bilateral cerebellar hemispheres. Results were largely independent of whether ADHD was ongoing (n=17) or had remitted (n=26), suggesting that many structural brain differences endure in individuals with a childhood history of ADHD, irrespective of current ADHD status in adulthood [30••].

Befitting its status as a neurodevelopmental disorder, ADHD investigators have increasingly focused on developmental trajectories. In this regard, the NIMH group has long been at the forefront. Most recently, they reported a significantly higher rate of growth in the most anterior region of the corpus callosum in 236 right-handed participants with ADHD than in 230 comparisons scanned at mean age 10, 12, 15, and 17 [18]. This study highlights the dynamic nature of ADHD-related structural abnormalities, which may reflect the changes in the clinical presentation of ADHD during development, although this hypothesis has not been directly tested. From a developmental perspective, we note the publication of the first study [23] examining regional cortical and subcortical brain volumes in preschool children with ADHD. Mahone et al. [23] found significantly reduced caudate volumes bilaterally in 11 medication-naïve preschoolers with ADHD vs. 13 comparisons (ages 4–5 years). Left caudate volume significantly predicted hyperactive/impulsive, but not inattentive symptom severity. As the sample size in this pioneering study was marginal, the lack of significant group differences outside the caudate should not be interpreted as definitive.

Because ADHD is increasingly conceptualized as a disorder of altered connections within and among neuronal networks, DTI studies have been conducted to assess possible structural anomalies in principal white matter tracts. A recent contribution [25•] reported the first DTI study conducted exclusively in prepubertal children who were largely medication free. Besides replicating previously reported structural anomalies in white matter tracts implicated in higher-order cognitive functions, Nagel et al. [25•] also found a novel alteration in the frontolimbic tract, which is implicated in emotional functions, in line with increasing clinical attention to emotional dysregulation in ADHD [46]. The authors noted that the frontolimbic tract is among the last WM tracts to mature and that developmental effects may be detectable in ADHD that are no longer observable in older children or adults. The authors also suggested that WM alterations may be an early marker of ADHD rather than reflecting compensatory restructuring. Another recent DTI study by Dramsdahl et al. [14] has extended our knowledge on WM abnormalities in adults, showing that, despite a lack of macrostructural abnormalities in the corpus callosum, DTI revealed ADHD-related microstructural abnormalities in the isthmus-splenium. Dramsdahl et al. [14] suggested that, although adults may have compensated for macrostructural callosal abnormalities often found in children, microstructural alterations that may explain impairments in auditory and speech perception functions subserved by fibers crossing the isthmus-splenium were still present. They noted that possible auditory and speech perception deficits are rarely considered when adults with ADHD are evaluated clinically.

Studies of DTI in children with ADHD have confirmed diffuse abnormalities in a large set of white matter clusters, rather than in restricted regions [27, 31]. The ADHD DTI literature has advanced sufficiently to support an initial meta-analysis. Pooling data from nine studies, Van Ewijk and colleagues [39••] reported consistent abnormalities in a large cluster in the right anterior corona radiata, in another cluster in the left cerebellar WM, and in additional clusters in the internal capsule. All the tracts identified meta-analytically connect brain areas implicated in the pathophysiology of ADHD.

Diffusion-based imaging methods are also being extended to extract even more information about brain microstructure. One such novel approach is referred to as diffusional kurtosis imaging (DKI), which uniquely enables quantification of the microstructural integrity of both gray and white matter, even in the presence of crossing fibers, a well known limitation of classic DTI. A preliminary application of DKI in 12 adolescents with ADHD and 13 typically developing children (TDC) found a lack of age-related increase of WM complexity in the ADHD group, in contrast with the TDC participants [19•].

A convergence of approaches has begun to illuminate the genetic and environmental causes of brain alterations. However, combining imaging and genetics methods requires substantial sample sizes. For example, de Zeeuw et al. [13•] were able to use a data set of over 300 to investigate the effects of prenatal exposure to cigarettes and alcohol in the context of ADHD. At mean age of ~10 years, ADHD children exposed antenatally to cigarettes had the smallest cerebellum volumes of the analyzed subgroups. Those with ADHD who had not been exposed to nicotine or alcohol prenatally had intermediate cerebellar volumes, and unexposed controls had the largest cerebellar volumes. The stair step pattern of results suggests that both genetic and environmental effects likely affect brain structure, and children with ADHD who are prenatally exposed to cigarettes or alcohol may suffer from a "double hit", with clear clinical and public health implications.

In summary, recent structural studies of ADHD have extended classical ADHD models of ADHD pathophysiology focused on cerebellar–frontal–striatal models by including a broader range of brain regions, including subregions within temporal and occipital cortex. Recent studies have extended the ages at which ADHD is examined to as young

as preschoolers and into middle-adulthood, and investigators are continuing to begin to investigate the genetic and/or environmental basis of the brain correlates of ADHD. As analytical methods continue to improve (e.g., Ref. [21]) we can expect further advances in our knowledge of the structural brain anomalies underpinning ADHD.

Functional Studies

Similarly to structural studies, functional studies of ADHD have primarily reported differences among groups; these are useful in advancing understanding of the underlying pathophysiology but which are not relevant to clinical practice. However, shifts in the conceptualization of ADHD, evolution of methods and analytical techniques, and collaborative efforts among scientists throughout the world are changing perspectives and bringing closer the time when functional imaging in ADHD will be relevant to day-to-day clinical practice. Specifically, the recent functional imaging literature has begun to address the hypothesis that at least some of the symptoms manifested by individuals with ADHD can be ascribed to abnormal regulation of large-scale brain networks, with much of the focus being placed on the brain's default network [47].

Functional imagers have recently taken note of the startling synchrony of brain regions even in the absence of specific cognitive or motor tasks. So-called resting state functional MRI (R-fMRI) consists in obtaining blood-oxygen level dependent (BOLD) signals for several minutes and then examining the patterns of synchronous intrinsic activity [47]. Such data are amenable to a wide range of analytical methods [47] which reveal large-scale brain networks that replicate across laboratories and that are substantially stable in test–retest analyses [49••]. The most frequently examined intrinsic brain connectivity network (also referred to as a "resting state network") was named the brain's default network (DN) by Raichle and colleagues [47]. The DN is defined by low-frequency synchronous spontaneous activity in medial prefrontal, medial parietal, lateral temporal, and medial temporal regions [49••]. The amplitude of DN fluctuations is systematically attenuated when attention is externally oriented and amplified during self-oriented processing or during task-unrelated thoughts [50]. Simultaneous observation of DN and fronto-parietal regions reveals a reciprocal pattern of activity—described as anticorrelations [51•]—which led Sonuga-Barke and Castellanos to propose the DN hypothesis of ADHD [52••]. They suggested the DN might be inadequately regulated by other task-active systems, and might consequently intrude on or disrupt ongoing cognitive performance, contributing to the spontaneous fluctuations in attention that appear to characterize ADHD. This hypothesis has begun to be examined directly, as we discuss below.

A meta-analysis of task-based fMRI studies published by the end of June 2011 [10••] showed that most of the hyperactivated regions in contrasts of ADHD vs. comparisons were located in the DN, as predicted by the DN hypothesis of ADHD. Other studies that were not included in the meta-analysis (because they were published after June 2011) are also germane. Sun at al. found reduced anticorrelation between the dorsal anterior cingulate cortex (dACC) (a component of the task-positive network) and the DN, replicating an initial observation in adults with ADHD [53•]. Liddle and colleagues [22••] showed that children with ADHD did not deactivate the DN during a task in relation to comparisons when off methylphenidate and under low motivational incentives, but the groups did not differ significantly when the ADHD children received high motivational incentives or were treated with methylphenidate. They concluded either motivational incentives or methylphenidate may normalize abnormal deactivation of the DN in ADHD.

Examination of the DN during rest was used to compare children with ADHD (n=37) and typically developing children (n=37) in relation to externalizing and internalizing scores on the Child Behavior Checklist [8]. On the one hand, significant associations were found between increasing internalizing scores and stronger positive intra-DN intrinsic functional connectivity (iFC), and between increased externalizing scores and reduced negative iFC between DN and task-positive regions such as dACC, irrespective of diagnostic group. On the other hand, some brain–behavior relationships differed between groups. Despite the exhortation that investigations of psychopathology should adopt a primarily dimensional approach [54••]; these data suggest that both dimensional and categorical approaches must be combined when developing mechanistic models of psychopathology. Still, the power of dimensional analysis was suggested by Shaw et al., who reported linear relationships between the rate of cortical thinning in TDC in relation to the extent of ADHD symptoms, from none, minimal, to moderate, with the rate approximating that of children with ADHD [36••].

Categorical contrasts among ADHD, autism spectrum disorders (ASD), and healthy comparisons (n=20 per group) found lack of suppression in the posterior node of the DN, in the precuneus, in both patient groups [9]. Within each group, precuneus activity was significantly negatively correlated with prefrontal activation, lending support to the DN hypothesis for both ADHD and ASD. Additionally, they found deficits that were disorder-specific. Specifically, left dorsolateral prefrontal cortex underactivation, which was related to task performance, was only found in ADHD. This study presages the upcoming revision of diagnostic criteria for ADHD in DSM-5 which are expected to allow the co-application of diagnoses of ADHD and ASD.

Another example of looking for common and unique results was conducted in 20 adults with ADHD and 24

comparisons who underwent fMRI with three tasks investigating interference inhibition, action withholding, and action cancellation. The last two tasks resulted in basal ganglia hypoactivation, whereas interference inhibition resulted in mid-cingulate and temporal lobe hypoactivations in ADHD. This study adds to the growing awareness that multiple neural networks implicated in ADHD can be identified via a range of task probes [34].

As noted in our review of structural studies, investigators have been increasingly focusing on emotional reactivity in ADHD. A functional comparison of 15 adolescents with ADHD and 15 healthy comparisons during subliminal presentation of fearful faces revealed atypical processing of fear in ADHD [28]. Adolescents with ADHD also had significantly greater effective connectivity between amygdala and lateral prefrontal cortex.

An impressive fMRI study examined both BOLD signal and skin conductance in 28 adults with ADHD and 28 comparisons using a card-guessing task in which incentive and outcomes were manipulated. This well-powered and rigorously designed study found that medial orbitofrontal cortex activation coded for reward value in controls but not in patients with ADHD [42••]. The imaging results were corroborated by findings on tasks of delay discounting and impulsive decision making. In patients with ADHD, neural signals in medial orbitofrontal cortex were dysregulated—overvaluing low-incentive rewards and undervaluing high-incentive monetary rewards. The authors conclude that these atypical patterns of neural behavior in a key circuit related to self-regulation and complex decision making are likely to be relevant to the emotional and motivational challenges encountered by adults with ADHD.

Although the bulk of functional imaging studies use MRI, PET and SPECT have an unarguable advantage for probing specific neural systems, for example dopaminergic function, in vivo [12]. Volkow et al. [40••] re-examined PET measures of D2/D3 receptor and dopamine transporter availability in the midbrain and nucleus accumbens and related these to a surrogate measure of motivation. They found disruption of the brain dopamine reward pathway in 45 adults with ADHD relative to 41 controls, which was related to symptoms of inattention in participants with ADHD, thus linking core symptoms of inattention to the broader concept of motivational processes in ADHD.

In summary, besides the classical task-based cross-sectional studies and PET/SPECT studies, the increasing number of resting state functional studies has the potential to provide a more comprehensive picture of the complexity of the networks involved in ADHD. In the near future, these can be expected to provide neuroimaging techniques to complement the diagnostic and prognostic process at the single subject level. As findings using expensive or invasive methods are increasingly validated, we expect that they will be extended to other approaches that may be more amenable to clinical settings. Two well-designed studies using functional near-infrared spectroscopy [32, 33] provide an illustrative early example of this process. Another preliminary report with possible clinical implications was that of Cortese et al., who contrasted 18 children with ADHD with 18 comparisons, half of whom were healthy, the other half with non-ADHD psychiatric conditions, on an MRI index of brain iron levels [11•]. They found significantly reduced T2* in bilateral thalamus which was interpreted as evidence of deficient brain iron, which is essential for myelination and monoaminergic metabolism. Confirmation of this pilot result with newer methods [55] would raise the issue of whether such brain iron abnormalities can be modified by dietary supplementation.

Neuroimaging Studies of ADHD Treatments

Studies of the mechanism of action of ADHD drugs or investigations assessing the brain correlates of ADHD treatments are of particular interest to clinicians. A preliminary meta-analysis of dopamine transporter availability, measured with PET or single-photon emission computed tomography [17•] tentatively concluded that reports of increased dopamine transporter availability in ADHD are likely to reflect a history of treatment with stimulants, rather than the neurobiology underlying the disorder. In related work, Volkow et al. showed that a challenge dose of 0.5 mg kg^{-1} intravenous methylphenidate significantly increased dopamine in striatum and these dopamine increases were associated with reductions in ratings of inattention [42••].

Normalization of medial prefrontal cortex activity by stimulant treatment was demonstrated by use of cognitive and emotional versions of the Stroop task for 15 adolescents with ADHD scanned both on and off medication [29]. Wong and Stevens conducted a randomized double-blind placebo-controlled trial in conjunction with fMRI during the Sternberg working memory task on 18 adolescents with ADHD [44]. They observed that methylphenidate leads to strengthened connectivity of some frontoparietal regions; this may be the basis of the improvement in reaction time observed during the working memory task.

Besides this body of research focusing on pharmacological treatment, we note a study showing volumetric gray matter increases in bilateral middle frontal cortex and right inferior–posterior cerebellum after cognitive training of 18 children with ADHD vs. 18 comparisons [20••]. Of note, gray matter volume increase in the inferior–posterior cerebellum was associated with improved attentional performance. If replicated independently with larger samples, these results would engender substantial enthusiasm.

Conclusions

The growing neuroimaging literature continues to contribute to models of the pathophysiological mechanisms underpinning ADHD. This maturing field provides substantial evidence implicating frontal-striatal and cerebellar regions in ADHD while also supporting the inclusion of interactions among extra-frontal regions detected during specific tasks or even during "rest."

Emerging results relevant to clinical practice include findings that many brain structural differences continue to be evident in ADHD in middle adulthood, irrespective of whether the disorder persists or has remitted [30••]. Such enduring alterations are likely ascribable to genetic factors, but they may also reflect prenatal exposure to, for example, nicotine or alcohol [13•]. Although randomized controlled long-term trials of stimulant treatment will never be conducted on humans, for obvious ethical reasons, indirect accumulating evidence suggests that stimulants normalize brain structure [16••, 26••] and function [22••] and that deviations from typical development are not the result of stimulant treatment [4].

One of the dividends of brain-imaging studies is the increasing awareness that brain correlates of emotional reactivity [28] and emotional processing [25•] are abnormal in groups of individuals with ADHD. Also novel, and based on imaging results, is the suggestion that auditory and speech perception deficits be considered in clinical and research evaluations of adults with ADHD [14]. Similarly, consistent, but heretofore ignored, findings of visual occipital cortex abnormalities in ADHD [3, 10••, 30••] imply that visual perception may be fruitfully reexamined in ADHD [48••].

Despite the increasing pace of progress in neuroimaging methods and approaches, claims of clinical utility of neuroimaging-based techniques are premature [56••] and currently indefensible for diagnosis of ADHD or for formulation of treatment plans. However, with continued momentum and widespread adoption of an ethos of open science [57••], we expect that imaging techniques will soon be able to support the clinical process, particularly for disambiguation of the most challenging cases.

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