Neuroimaging in attention-deficit/hyperactivity disorder

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Purpose of review
Neuroimaging research on attention-deficit/hyperactivity disorder (ADHD) continues growing in extent and complexity, although it has yet to become clinically meaningful. We review recent MRI research on ADHD, to identify robust findings, current trends and challenges.

Recent findings
We identified 40 publications between January 2019 and September 2020 reporting or reviewing MRI research on ADHD. Four meta-analyses have presented conflicting results regarding across-study convergence of functional and resting-state functional (fMRI and R-fMRI) studies on ADHD. On the other hand, the Enhancing NeuroImaging Genetics Through Meta-Analysis international consortium has identified statistically robust albeit small differences in structural brain cortical and subcortical indices in children with ADHD versus typically developing controls. Other international consortia are harnessing open-science efforts and multimodal data (imaging, genetics, phenotypic) to shed light on the complex interplay of genetics, environment, and development in the pathophysiology of ADHD. We note growing research in 'prediction' science, which applies machine-learning analysis to identify biomarkers of disease based on big data.

Summary
Neuroimaging in ADHD is still far from informing clinical practice. Current large-scale, multimodal, and open-science initiatives represent promising paths toward untangling the neurobiology of ADHD.

Keywords
attention-deficit/hyperactivity disorder, MRI, neuroimaging, personalized medicine

INTRODUCTION

More than 25 years of neuroimaging studies on attention-deficit/hyperactivity disorder (ADHD) have yielded a few apparently firm findings and many open questions. The long-term objective is to uncover the underlying pathophysiology to reveal reliable biomarkers of prognosis and treatment response, that is personalized medicine [1]. Unfortunately, ADHD neuroimaging research, as for other psychiatric disorders, is still unable to inform clinical practice [2].

The neuroimaging literature on ADHD is voluminous and inconclusive. As of September 30, 2020, PubMed contained 1962 papers identified with the search terms 'ADHD' and 'MRI'. Here, we offer a brief narrative review of recent studies using structural and functional MRI in patients with ADHD; given the conflicting literature, we focus on meta-analyses, mega-analyses, and novel multimodal methods being proposed to parse brain-behavior relationships in multidimensional space.

TEXT OF REVIEW

Literature review: methodology

We systematically searched original research and reviews published between January 1, 2019, and September 30, 2020, in PubMed and Ovid with the terms: 'ADHD' or 'attention deficit hyperactivity disorder' and 'neuroimaging'. We identified 110 unique articles, from which both authors independently

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KEY POINTS

- Neuroimaging research literature on ADHD continues to grow, and the last 21 months have seen progress in statistical power, multimodal integration, and technical complexity.
- Meta-analyses of functional neuroimaging research have failed to provide spatial convergence across studies, with the exception of meta-analysis focused on a few networks of interest.
- The ENIGMA consortium is providing more robust evidence about small but significant structural brain differences between children with ADHD and typically developing controls. Other multimodal 'big data' consortia are providing promising results linking genetics, brain, and phenotypes.
- Machine-learning approaches hold promise to identify multimodal markers related to the diagnosis and prognosis of ADHD, although methodological challenges need to be addressed.
- Neuroimaging in ADHD is still unable to inform clinical practice; wider implementation of open science and best practices in conducting and reporting research in big and small endeavors is needed.

screened and selected 40 publications on MRI research in ADHD, among which we describe those we believe most relevant in describing the state of the art.

Systematic reviews and meta-analyses: seeking convergence and understanding heterogeneity

Meta-analyses of imaging studies pool brain coordinates to determine whether spatial findings converge beyond chance. For example, activation likelihood estimation (ALE) assumes a spatial gaussian distribution around each reported activation peak and models how often such loci should overlap under the null hypothesis [3]. Because the ALE algorithm requires the input of loci yielding significant group differences, most sample sizes are small, and negative results are less likely to be published, this process is biased towards false positives. This may explain conflicting spatial locations and directions of differences across studies. To wit, recent ADHD meta-analyses conducted at the whole-brain level have largely concluded that findings in structural MRI, task-based MRI (fMRI), and resting state fMRI (R-fMRI) do not currently converge spatially across studies [4▪▪,5▪▪].

Specifically, Samea *et al.* [4▪▪] sought to build on a prior positive meta-analysis of 55 fMRI studies [6]. They pooled 96 studies (22 structural, 68 fMRI, and 6 R-fMRI) in children and adolescents, comprising 1914 unique participants. Disappointingly, their main analyses failed to find spatial convergence across studies and modalities. Prior positive fMRI results [6] were ascribed to a software bug in an earlier version of the ALE code which produced overly liberal multiple comparison corrections [4▪▪]. Focusing exclusively on R-fMRI, Cortese *et al.* [5▪▪] meta-analyzed 30 R-fMRI studies comparing children, adolescents, and adults with ADHD versus typically developing control individuals (TDCs), and obtained negative results on multiple intrinsic functional connectivity metrics.

By contrast, two meta-analyses of R-fMRI studies restricted to specific brain networks reported positive results. Gao *et al.* [7▪] meta-analyzed 21 studies including 700 patients with ADHD and 580 TDCs, using anisotropic effect-size seed-based d-mapping (AES-SDM), which includes both positive and null results. Their analyses of seed-based correlation studies (i.e., measuring functional connectivity between preselected brain areas, named 'seeds', and any other area) were limited by the data available to seeds in the default mode, frontoparietal, and affective networks. Overall, their findings supported a 'triple network' model proposed for ADHD and other neuropsychiatric disorders [8], with putative dysfunctional interactions among the default, frontoparietal, and salience/ventral attention networks [8] in patients versus controls.

Sutcubasi *et al.* [9▪] meta-analyzed a partly-overlapping set of 20 studies including 944 patients with ADHD and 1121 TDCs, using multilevel kernel density analysis using contrasts/studies as units of analysis. Their correlation analyses were restricted a priori to seeds in the default mode, cognitive control, salience, and affective/motivational networks. Results supported the default network interference hypothesis of ADHD [10], which attributes ADHD symptoms to dysfunctions within the default network and its interplay with 'task-positive' networks.

Divergent results from three meta-analyses [5▪▪,7▪,9▪] with mostly overlapping input data raises many questions. Although methodological differences likely contribute, their contrasts may also reflect using a fully data-driven method [5▪▪] versus analyses limited to four [9▪] or three network seeds [7▪]. We note the negative analysis [5▪▪] included multiple R-fMRI indices to address the 'looking under the lamppost' bias. All three studies concluded that the R-fMRI literature is still developing, with insufficient numbers of original studies, most with small, underpowered samples. Thus, any conclusions regarding intrinsic functional connectivity remain tentative. By contrast, the issue of statistical

power in brain structure studies is being addressed by mega-analyses.

Enhancing NeuroImaging Genetics Through Meta-Analysis: identifying small but consistent differences in brain structure

The Enhancing NeuroImaging Genetics Through Meta-Analysis (ENIGMA) project has created open international consortia, building on original efforts to leverage large-scale collections of genetic and neuroimaging data [11]. ENIGMA embodies global open-science, comprising multiple study groups, including one focused on ADHD [12]. This group currently includes 36 centers in Europe, USA, Australia, China, and Brazil, which have locally analyzed cross-sectional MRI data from thousands of participants with identical FreeSurfer software. The resulting brain indices (e.g., thickness, volume, surface area) can then be aggregated centrally without threatening participant confidentiality.

In the first ENIGMA publication on ADHD [13], differences in global intracranial and subcortical gray matter volumes were documented in 1713 patients with ADHD versus 1429 age-matched TDCs. In omnibus analyses, patients had smaller global intracranial volume, and smaller volumes of accumbens, amygdala, caudate, hippocampus, and putamen, albeit with small effect sizes (Cohen's *d* between 0.1 and 0.19). Nearly all differences were only present in children (versus adolescents or adults) with ADHD. A subsequent effort examined cortical thickness and surface area: in 2246 patients with ADHD (74% male) versus 1934 TDCs (60% male), ages 4–63 (mean age ~11), smaller surface areas were found widely, particularly in frontal, cingulate, and temporal cortices, and thinner cortex in the fusiform gyrus and temporal pole in children with ADHD versus age-matched TDCs [14▪]. Once again, adolescents and adults with ADHD showed no reliable differences from TDCs.

ENIGMA studies have also contrasted regional cortical volumes versus TDCs in six psychiatric disorders including ADHD [15], and subcortical brain volumes, regional cortical thickness, and cortical surface areas among ADHD, autism spectrum, and obsessive-compulsive disorders [16]. Both studies found that ADHD (and autism spectrum disorder) presented unique patterns of brain structural abnormalities distinct from one another and from patterns common to the others.

The ENIGMA studies, which continue to emerge, demonstrate that large multicenter collaborations can provide well powered samples for cross-sectional neuroimaging analyses; development matters, as statistically significant differences in ADHD have been almost exclusively limited to children, for reasons that remain unexplained; despite genetic risk loci not differentiable with other psychiatric disorders, ADHD exhibits unique patterns of volumetric abnormalities; and reliable differences in brain structure between patients with ADHD and TDCs have small effect sizes ($0.10 < d < 0.3$). These humbling findings are consistent with the small effect sizes of genome-wide significant results [17], reflecting the multidimensionality of complex disorders [18]. Nevertheless, such findings set a floor on the scale of future studies seeking definitive results.

Brain imaging and genetics: the promise of multimodal studies

Longitudinal, multicenter, and open-science efforts are increasingly seeking to integrate imaging, genetic and phenotypic data, exploring the intermediary ('mediator') role of neuroimaging in transducing genetic load (quantified as polygenic risk scores (PRS), the cumulative effect of common DNA variants associated with a given disorder [19]) into clinical symptoms. Such approaches can also be applied to TDCs, assuming linearity across the clinical continuum, an assumption of the Research Diagnostic Criteria (RDoC) initiative [20].

The IMAGEN consortium comprises a longitudinal, sex-balanced cohort of ~2000 nonclinically ascertained adolescents from eight European centers [21]. These data allowed Barker *et al.* [22] to report an association between ADHD PRS (from the first ADHD genome-wide significant findings) [17] with impulsivity and body mass index phenotypes, mediated by grey matter volumes (in bilateral cerebellum, amygdala, hippocampus, parahippocampus, and orbital frontal cortex), and by function on a monetary incentive delay fMRI task (in fusiform gyrus and parahippocampus, postcentral and parietal inferior, calcarine and occipital superior, and frontal superior medial cortices). Albaugh *et al.* [23] examined diffusion tensor imaging and cortical thickness and found a small effect size association between ADHD PRS, ADHD symptoms, and fractional anisotropy in bilateral superior and inferior longitudinal fasciculi; cortical thickness indices were not associated with PRS.

Other relevant community samples include Generation R, a birth cohort of Rotterdam children in which higher ADHD PRS was associated with smaller caudate volume, which mediated the relation between PRS and inattention symptoms in 1139 10-year-old participants [24]. Stojanovski *et al.* [25] sought gene-imaging associations with ADHD symptoms in 3611 individuals with or without a history of traumatic brain injury (TBI) in the

Philadelphia Neurodevelopmental Cohort. Caudate volume mediated the negative association between PRS and ADHD symptoms regardless of TBI, but corpus callosum genu fractional anisotropy was only related to ADHD symptoms in those without TBI, suggesting distinct genetic and environmental pathways to ADHD symptoms.

Multimodal approaches have also been applied to samples of patients with ADHD. Hermosillo *et al.* [26] examined the association between PRS and R-fMRI intrinsic functional connectivity in amygdala, accumbens, and caudate in 196 patients with ADHD and 119 TDCs (mean age ~10 years) from the Psychiatric Genomics Consortium. Two functional connectivity circuits (right caudate and parietal cortex; accumbens and occipital cortex) were correlated with both PRS and diagnostic status (ADHD vs. TDC).

Finally, Ing *et al.* [27▪] examined the IMAGEN dataset to identify structural (anatomic MRI and diffusion tensor imaging) and R-fMRI correlates of two transdiagnostic constructs, anxiety/depression and executive dysfunction, in healthy individuals at age 19. Anxiety/depression was associated with decreased grey matter volume in the middle temporal gyrus, reduced fractional anisotropy in the corpus callosum genu, and increased functional connectivity between default mode network and cerebellum. Executive dysfunction was associated with decreased grey matter in right middle temporal gyrus. They replicated the discovered neurobehavioral associations in patients with ADHD, major depressive, bipolar, and schizophrenia disorders in the NeuroIMAGE clinical cohort [28]. In an ADHD subanalysis (including 184 patients, 103 unaffected siblings, and 128 TDCs), they found significant smaller grey matter volumes in patients versus TDCs in the brain areas they previously associated to anxiety/depression ($d = 0.26$) and executive dysfunction ($d = 0.32$).

Analyses of multimodal neuroimaging, genetics, and dimensional phenotypes require leveraging increasingly powerful computational methods, which we now briefly mention.

Machine learning to predict diagnosis and prognosis of attention-deficit/hyperactivity disorder

Machine learning methods are increasingly being used to discriminate between patients with ADHD and TDCs and to predict future clinical outcomes, including treatment response [29▪]. For instance, Yoo *et al.* [30▪] integrated multimodal neuroimaging (structural MRI, diffusion tensor imaging, fMRI, and R-fMRI) with genetic, clinical, and neuropsychological data to distinguish children with ADHD from TDCs. Although several imaging findings were promising in 'predicting' clinical scores and task performance (with 85% accuracy), their data were cross-sectional, the training and validating datasets were small (47 and 18 per group, respectively), and, unsurprisingly, genetic data did not contribute to their predictive models. Other recent efforts using the open-access 'ADHD-200' data include Itani *et al.*, who implicated the limbic system in the pathophysiology of ADHD [31], and Riaz *et al.*, who instead highlighted the frontal lobes [32].

Of note, although published studies report high accuracy values (median ~78%, range 54–100%) [29▪], concerns have been raised about their methodological robustness. Pulini *et al.* [33▪] reviewed 69 machine-learning classification/prediction neuroimaging studies in ADHD and noted that circular analysis and small sample sizes inflate classification accuracies and that many studies lack internal and external validation. Circular analysis refers to using the same, or overlapping, samples to train and test classification algorithms, biasing their accuracy, whereas lack of validation (i.e., testing algorithm performance in new subjects, either within the study population – internal – or in other populations – external) limits generalization of prediction models beyond included subjects. They estimated that diagnostic prediction accuracies in studies with low risk of circularity biases should range between 60 and 80%, with sample size and accuracy negatively correlated.

Other active areas of research

We note in passing other themes in the recent ADHD literature including the different presentations (formerly subtypes) [34,35] and the overlap/comorbidity with reading [36,37] and autism spectrum [38,39] disorders.

Where is the field going?

Neuroimaging research in psychiatric disorders, including ADHD, is still in its infancy. The crisis of reproducibility in science extends beyond neuroimaging, but it certainly also applies here [40]. We take the view that optimistic expectations are nearly always required to motivate extraordinary novel initiatives, with the human genome project a recent example. The early claims about the benefits of mapping human DNA were overblown, yet the recent products have been innumerable. Some lessons from genetics/genomics bear examining. After initial non-replications of small-scale studies, the criterion of independent replication prior to publication of purportedly definitive results emerged. Crucially, the principal funders of genetic studies insisted on full

open sharing of genetics data, uploaded nightly, rather than 'after the data have been cleaned' and published. This culture change made it possible to aggregate datasets of tens of thousands while genotyping costs dropped precipitously. Such improvements in cost/efficiency have not yet affected the acquisition of MRI data, which remains expensive [41]. Eventually, novel low cost imaging technologies may revolutionize structural imaging, although their potential impact is just now being explored [42].

Beyond the large-scale efforts we have briefly described, harmonized multicenter data acquisition with open data sharing will increase in importance. The Adolescent Brain Cognitive Development (ABCD) study, although not specifically focused on ADHD, included more than a thousand children with ADHD at inception, who are being scanned every two years from ages 9 to 20 [43]. NIH Report lists a new research project (R01MH123831) begun in June 2020 focused on ADHD using ABCD. This and similar studies will produce well powered insights into the neurobiology of ADHD during the second decade of life. Increasing emphasis on sharing of data and analytic scripts will help assure that results are replicable [44], even if they also yield small effects.

It is notable that most studies take as their starting points the identification of reliable differences between patients with ADHD and TDCs. This strategy is often interpreted as reflecting the desirability of obtaining objective diagnostic criteria. We disagree. For example, although cystic fibrosis was the first genetic disorder to be 'solved,' the diagnosis remains primarily clinical, because no single laboratory can test all the rare variants that contribute to the 30% of cases not because of the single most frequent mutation. The rationale for pursuing neuroimaging studies in psychiatric conditions is to move closer to identifying the diverse pathophysiologies that underlie the clinical heterogeneity we observe. From that perspective, it is felicitous that neuroimaging studies seem to support the relevance of large-scale neuronal networks for models of brain function [45▪]. Fortunately, achieving cellular levels of resolution is not necessary or even useful for progressing in our understanding of brain function.

On the other hand, we do not believe that one-size-fits-all templates of large-scale brain networks (or templates for specific ages in childhood [46]) will suffice. They represent a crucial intermediate step in a process that is moving towards single-subject analyses, without smoothing [47].

Even when native-space, unsmoothed imaging becomes practical, addressing developmental questions will remain challenging. Structured hierarchical designs, which combine cross-sectional and longitudinal approaches, are essential to resolve differences between children and adults with ADHD. An example of this approach, not yet applied to clinical questions, was presented by Vasa *et al.* [48] in a cross-lag sample of 298 healthy individuals between 14 and 26 years-of-age, with state-of-the-art methods to decrease the effects of head motion. They found two types of trajectories in functional connectivity, 'conservative' or 'disruptive'. Specifically, motor networks were conservative (i.e., their functional connectivity, already strong at adolescence, increased through young adulthood), whereas cortical-subcortical connections, especially association, default mode, frontoparietal, and limbic networks tended to be disruptive (i.e. either their weak functional connectivity at adolescence strengthened, or their strong functional connectivity at adolescence decreased over that age span) [48]. Such dissociations, if replicated, would allow stratification of brain circuit trajectories, the most cost-effective means to dramatically increase statistical power. Determining which of these trajectories typifies ADHD development will be important.

Although we are in the era of big data, 'small science' research (i.e., local studies with moderate numbers of participants) is still needed to develop novel methods, determine feasibility, and support the career development of junior investigators [49]. Both types of studies must embrace transparency and reproducibility, including preregistration of hypotheses and data analytic plans [44].

CONCLUSION

Neuroimaging research on ADHD since 2019 has documented that children with ADHD have smaller global and regional brain structural indices than TDCs, in both cortical and subcortical areas, albeit with small effect sizes. Functional imaging results are less clear; some meta-analytic approaches suggest interplay of several key networks is associated with ADHD; this conclusion was not supported by the most comprehensive and unrestricted analyses. Multimodal approaches integrating imaging, genetic, and phenotypic data are emerging, although their replicability has yet to be confirmed. Adoption of open science and best reporting practices are needed to make ADHD neuroimaging research more methodologically sound and relevant to improve the care of patients.

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Conflicts of interest

The authors of this manuscript have nothing to disclose.

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