Neuroimaging in Attention-Deficit/Hyperactivity Disorder: Recent Advances

Fatemeh Dehghani Firouzabadi, MD[1,2], Sara Ramezanpour, MD[3], Mohammad Dehghani Firouzabadi, MD[1,2], Ilyssa J. Yousem, MEd, MS[4], Nicolaas A. J. Puts, PhD[5,6], David M. Yousem, MD, MBA[7]

Neuroradiology/Head and Neck Imaging · Review

Keywords

attention-deficit/hyperactivity disorder, brain, MRI, MR spectroscopy, PET

F. D. Firouzabadi and S. Ramezapour contributed equally to this work.

Submitted: May 27, 2021
Revision requested: Jun 11, 2021
Revision received: Jul 26, 2021
Accepted: Aug 9, 2021
First published online: Aug 18, 2021

The authors declare that they have no disclosures relevant to the subject matter of this article.

An electronic supplement is available online at doi.org/10.2214/AJR.21.26316.

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental condition that leads to impaired attention and impulsive behaviors diagnosed in, but not limited to, children. ADHD can cause symptoms throughout life. This article summarizes the structural (conventional, volumetric, and diffusion tensor imaging) and functional (task-based functional MRI [fMRI], resting-state fMRI, PET, and MR spectroscopy) brain findings in patients with ADHD. Consensus is lacking regarding altered anatomic or functional imaging findings of the brain in children with ADHD, likely because of the heterogeneity of the disorder. Most anatomic studies report abnormalities in the frontal lobes, basal ganglia, and corpus callosum; decreased surface area in the left ventral frontal and right prefrontal cortex; thinner medial temporal lobes; and smaller caudate nuclei. Using fMRI, researchers have focused on the prefrontal and temporal regions, reflecting perception-action mapping alterations. Artificial intelligence models evaluating brain anatomy have highlighted changes in cortical thickness and the shape of the inferior frontal cortex, bilateral sensorimotor cortex, left temporal lobe, and insula. Early intervention and/or normal brain maturation can alter imaging patterns and convert functional imaging studies to a normal pattern. Although imaging findings provide insight into the neuropathophysiology of the disease, no definitive structural or functional pattern defines the disorder from a neuroradiologic perspective.

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that affects 2.5–9% of the population worldwide [1]. The disorder, with a male-to-female predilection of 2–4:1, is usually diagnosed in children on the basis of criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5), which requires documentation of six or more symptoms of either inattention or hyperactivity that persist for 6 months in two settings. For individuals older than 17 years old, the diagnosis requires documentation of five symptoms that impact academic, social, or occupational functioning. The more inclusive criteria that accompanied the transition from the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, to the DSM-5 in 2013 yielded an increased rate of diagnosis of ADHD [1–4]. The diagnosis is categorized into three types: predominantly inattentive/distractible presentation (ADHD-I), predominantly impulsive/hyperactive presentation, and the combined presentation of both inattention and hyperactivity (ADHD-C) (Tables 1 and 2).

Manifestations of inattention and hyperactivity include maladaptive behaviors (e.g., oppositional behavior, defiance, and hostility), inappropriate social interactions (e.g., impul-

[1]Endocrinology and Metabolism Research Center (EMRC), Vali-Asr Hospital, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.

[2]ENT and Head & Neck Research Center, The Five Senses Institute, Iran University of Medical Sciences, Tehran, Iran.

[3]Department of Radiology and Biomedical Imaging, University of California, San Francisco, San Francisco, CA.

[4]Behavioral Framework, Rockville, MD.

[5]Department of Forensic and Neurodevelopmental Sciences, Sackler Institute for Translational Neurodevelopment, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London, United Kingdom.

[6]MRC Centre for Neurodevelopmental Disorders, King's College London, London, United Kingdom.

[7]Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins Medical Institution, 600 N Wolfe St, Phipps B112D, Baltimore, MD 21287. Address correspondence to D. M. Yousem (dyousem1@jhu.edu).

ARRS is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education activities for physicians. The ARRS designates this journal-based CME activity for a maximum of 1.00 AMA PRA Category 1 Credits™ and 1.00 American Board of Radiology©, MOC Part II, Self-Assessment CME (SA-CME). Physicians should claim only the credit commensurate with the extent of their participation in the activity. To access the article for credit, follow the prompts associated with the online version of this article.

doi.org/10.2214/AJR.21.26316
AJR 2022; 218:321–332
ISSN-L 0361–803X/22/2182–321
© American Roentgen Ray Society

sivity, failure to take part in leisure activities quietly, and excessive talking), and learning impairments (e.g., failure to understand tasks or instructions as well as difficulty organizing tasks and activities) [5]. Patients with ADHD are also at higher risk for long-term illicit substance use and criminal activity [6]. Depression, oppositional defiant or conduct disorder, and anxiety are common psychologic comorbidities in ADHD [4, 6, 7]. Despite the variable course of the disease, nearly two-thirds of patients with ADHD can become asymptomatic with appropriate treatment [8].

Although ADHD was initially characterized as a pediatric disease, studies suggest that approximately 64% of children with ADHD carry symptoms into adulthood [9]. Moreover, studies of adults with newly diagnosed ADHD show that some did not manifest overt symptoms of ADHD in childhood [9, 10]. ADHD is estimated to affect 2.5–7.1% of adults who seek psychiatric help [9, 10].

Although neuroimaging has been used extensively in neuroscience publications on ADHD, the knowledge and discoveries resulting from such investigations have not yet been fully incorporated into radiologists' practice. This review describes the imaging findings of ADHD, including MRI, functional MRI (fMRI), diffusion tensor imaging (DTI), MR spectroscopy (MRS), and PET. The current status of machine learning and artificial intelligence (AI) for distinguishing patients with ADHD from typically developing children and children with other developmental disorders is also considered.

HIGHLIGHTS

- *Patients with ADHD differ from children with typical development in broad aspects of brain volumetry, functional neuroimaging, white matter connectivity, and CNS metabolites.*
- *Identification of specific imaging biomarkers of ADHD is challenged by normal brain maturation across the age spectrum, disease heterogeneity, ADHD subtypes, and neuropsychologic comorbidity.*
- *Artificial intelligence techniques offer the opportunity, based on well-characterized homogeneous study samples, for neuroimaging to become more definitive in diagnosing ADHD and its subtypes.*

Structural Imaging Findings

The behavioral changes occurring in early childhood in patients with ADHD may lead to a pediatrician ordering a clinical MRI examination to assess for structural causes of cognitive or neurobehavioral dysfunction. Alternatively, patients with ADHD may be enrolled in research protocols studying ADHD and related disorders. Although the former rarely leads to actionable findings, research studies have yielded group-based anatomic alterations and differences in functional networks and pathways [11]. Table S1, a supplemental table that can be viewed in the *AJR* electronic supplement to this article, available at doi.org/10.2214/AJR.21.26316, summarizes representative studies of different imaging techniques used to evaluate brain findings in ADHD.

Conventional MRI

The findings of brain MRI examinations performed in the clinical setting for patients with ADHD are most commonly interpret-

TABLE 1: Criteria for Diagnosis of Attention-Deficit/Hyperactivity Disorder

Type of Criteria	Symptoms
Inattention[a]	Is easily distracted or drawn into unrelated thoughts Does not pay close attention to details or makes careless mistakes Seems not to listen when directly spoken to Fails to follow instructions and finish assigned tasks Loses items needed for daily activities Has trouble holding attention when engaged in tasks or play activities Has trouble with task or activity organization Shows reluctance, avoidance, or dislike of tasks that require mental effort over an extended time Forgets easily
Hyperactivity and impulsivity[a]	Answers questions before the questioner has finished speaking Has trouble with waiting to take a turn Intrudes in other people's activities or interrupts their conversations Fidgets and/or taps hands and/or feet and squirms when seated Stands up when expected to remain seated Runs or climbs at inappropriate times (adults or adolescents may feel restless) Talks excessively Makes unacceptable levels of noise when playing Displays excessive levels of activity
Additional criteria[b]	Several symptoms occur in more than one setting Several symptoms in the inattention or hyperactivity and impulsivity categories were seen when the patient was younger than 12 years old Symptoms interfere with or lower quality of functioning in social, academic, or professional activities Symptoms occur outside of the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder

Note—The criteria described in this table are based on those in the *Diagnostic and Statistical Manual of Mental Disorders,* 5th edition, as described by Reynolds and Kamphaus [93].

[a]For children younger than 16 years old, six or more criteria must be met. In adolescents and adults, five or more criteria must be met. Each symptom must be present for at least 6 months.

[b]All four of these criteria must be met in addition to the required number of criteria for inattention and/or those for hyperactivity and impulsivity.

TABLE 2: Subtypes of Attention-Deficit/Hyperactivity Disorder (ADHD)

Type	Signs and Symptoms
Inattentive-type ADHD	Short attention span Easily distracted Being unable to pay close attention to details Difficulty listening when being spoken to Forgetful when performing everyday activities Often careless and constantly losing things like keys, books, and phones Struggles with engaging in organized tasks and activities Finds it difficult to follow instructions
Impulsive/hyperactive-type ADHD	Interrupting or intruding on others Acting without thinking Being impatient and having difficulty waiting their turn Blurting out the answer to a question before it has been completed Restlessness Talking excessively Being unable to focus on one task at a time Excessive fidgeting Being unable to engage in any activities quietly
Combined-type ADHD[a]	All of the aforementioned symptoms

Note—The contents of this table are based on information presented on the Cleveland Clinic website [94].
[a]ADHD with combined presentation of both inattention and impulsivity/hyperactivity.

ed as normal. Potential changes in cortical thickening and altered white matter volume [12, 13] are subtle and are typically detected only by use of dedicated research protocols. The most common alterations are in the left (in children) and right (in adults) frontal and prefrontal cortexes and medial temporal lobe cortex, which exhibit reduced cortical thickening and surface areas [12, 14–16]. Reductions in white matter volume in the frontal lobes are present but usually are not apparent on visual inspection, even when conducted by skilled pediatric neuroradiologists [12, 15].

Volumetric MRI

Various volumetric programs have been used to identify signature structural findings that suggest a diagnosis of ADHD [17–19]. These volumetric programs evaluate gray and white matter thicknesses, gyral surface area, cortical shape changes, and white matter volume. The most consistent finding is reduced frontal lobe volume, with reduced gyrifications and surface area [16–24]. A recent study described an association between smaller frontal lobe volume and reading disorders in individuals with ADHD [25]. Smaller nucleus accumbens, amygdala, caudate, hippocampus, putamen, and parahippocampal and temporal gyri have also been reported [19, 26].

A large clinical population-based study showed smaller surface area in frontal, temporal, and cingulate regions, especially in young children with ADHD. A thinner temporal pole and fusiform gyri were found in children with ADHD who were 10–11 years old [27].

Although these studies reported reduced volumes, other authors found greater gray matter volume in the intracalcarine and temporal cortexes [15] (Fig. 1) and in the left frontal eye fields of some patients [14, 15]. Caudate nucleus volume and right-left asymmetry have been investigated [17, 20, 21, 28–30], resulting in variable reports of right caudate volume reduction [20, 28, 30] and left caudate volume reduction [17, 21, 29].

In 2021, the ENIGMA-ADHD Working Group reported volumetric changes in a combined cohort of 1933 patients with ADHD and 1829 healthy control patients who were analyzed using Freesurfer software (version 7.1.0, Laboratory for Computational Neuroimaging) [31]. The study focused on right-left asymmetries in ADHD and found no strong right-left asymmetries that distinguished children with ADHD from control patients. Greater right-sided surface area reductions were observed in the right hemisphere in general and the orbitofrontal region more specifically. The cortical thicknesses of the right superior temporal gyrus, left caudal middle frontal cortex, left precentral gyrus, and left insula showed equivocal reductions in children with ADHD. In adults, only the left globus pallidus volume was reduced in ADHD. Across all age groups, after corrections for multiple comparisons, no asymmetry effects were noted. Coexistent mood disorder with ADHD was correlated with rostral middle frontal gyrus thickness. The authors concluded that, after false discovery rate statistical correction was applied, "all effects remained tentative, even in this unprecedented sample size…altered brain asymmetry is unlikely, in itself, to be a useful biomarker or clinical predictor of ADHD" [31].

In summary, volumetric brain studies of patients with ADHD show overall decreases in gray matter volume that most commonly occur in the frontal lobes as well as greater severity of symptoms in patients with smaller frontal and temporal lobe gray matter volume. However, the largest study of volumetry in ADHD, the multiinstitutional ENIGMA-ADHD Working Group study, fails to support findings in smaller cohorts.

Voxel-Based Morphometry

Voxel-based morphometry (VBM) graphically shows how two or more groups differ on the basis of standardized anatomic models. VBM studies have largely confirmed previously described differences in frontal and temporal lobe structures. Studies that found temporal lobe changes focused on the medial and superior temporal gyrus and hippocampus, whereas studies that found frontal lobe changes focused on the frontobasal regions, right orbitofrontal cortex, and the superior longitudinal fasciculus [18, 22].

Behavior-based VBM studies have shown a significant association between reduced gray matter volume of the left anterior

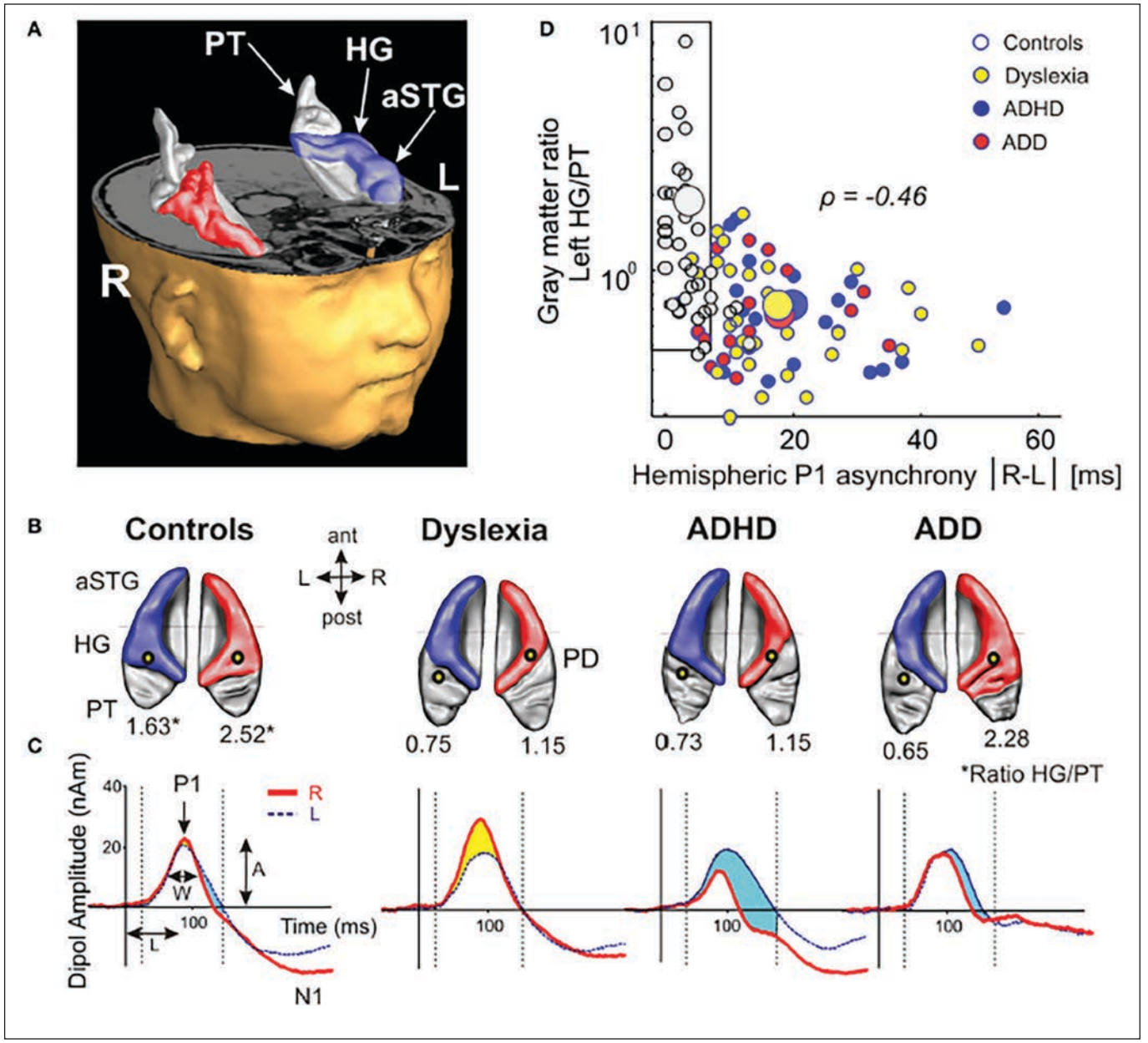


Fig. 1—Structural and functional auditory-related neuromarkers of dyslexia, attention-deficit/hyperactivity disorder (ADHD), and attention deficit disorder (ADD). R = right, L = left. (Image reprinted and legend adapted from Serrallach B, Groß C, Bernhofs V, et al., doi.org/10.3389/fnins.2016.00324, © 2016 Serrallach B, Groß C, Bernhofs V, Engelmann D, Benner J, Gündert N, Blatow M, Wengenroth M, Seitz A, Brunner M, Seither S, Parncutt R, Schneider P, Seither-Preisler A, subject to terms and including disclaimer in Section 5 of Creative Commons Attribution 4.0 International Public License, creativecommons.org/licenses/by/4.0/legalcode)

A, Three-dimensional reconstruction of patient. Heschl gyrus (HG), its duplications, and anterior superior temporal gyrus (aSTG) are shown in blue in left hemisphere and in red in right hemisphere. Planum temporale (PT; posterior triangular structure) and planum polare (anterior to first transverse sulcus) are shown in gray.

B, Diagrams show top view of group-averaged auditory cortexes. Left hemisphere (*blue area*) is characterized by PTs that are relatively larger (group average, 5703 mm^3) than those in right hemisphere (*red area*) (3662 mm^3). Values followed by asterisks indicate average ratios of gray matter volume of HG to gray matter volume of PT (ratio HG/PT) for groups and hemispheres. In left hemisphere, patients in all disorder subgroups showed oversized PTs and downsized HGs compared with control patients, resulting in diminished left hemisphere ratio HG/PT. However, only dyslexic children and children with ADHD were characterized by enlarged right PTs and, consequently, lower right HG/PT ratios. In contrast, patients with ADD did not show any right-hemispheric volumetric anomalies. Sources of primary P1 (most positive amplitude reached between 70 and 130 ms) responses to acoustic stimulation are projected onto group-averaged surface meshes (*yellow circles*). Although for control patients P1 sources localize robustly on HG in left and right hemispheres, patients in all disorder subgroups show atypical left-hemispheric focus of activation with more posterior P1 source in PT. ant = anterior, post = posterior, PD = posterior duplications (31 patients had dyslexia characterized by presence of complete posterior right HG duplications).

C, Group-averaged P1 source waveforms in response to sounds of various musical instruments and artificial tones for right (R; *red curve*) and left (L; *blue curve*) hemisphere. In contrast to control patients, patients in all three disorder subgroups showed considerably different bilateral activation patterns (*yellow* and *blue areas* denote stronger right- and left-hemispheric activation, respectively). Usually, P1 response was delayed on left side; however, 23% of children showed reversed pattern. We therefore calculated absolute P1 asynchrony (|R–L|) as general measure of bihemispheric latency divergence. Control patients showed well-balanced response patterns with mean absolute P1 asynchrony of 3.7 ms, whereas patients in all three disorder subgroups showed asynchronies that were approximately five times larger (patients with ADHD, 19.4 ms; patients with ADD, 17.5 ms; patients with dyslexia, 16.5 ms). Black "L" denotes length, and area between two vertical dotted lines denotes positive waveform. W = full-width half maximum, A = positive amplitude of waveform, N1 = most negative amplitude reached between 130 and 200 ms.

D, Correlation between relevant neuroanatomic and functional measures, left HG/PT ratio, and absolute P1 asynchrony, which together allow almost perfect separation of control patients (*gray circles*) and pooled disorder group (*colored circles*). Large symbols indicate mean values.

prefrontal cortex and worse emotional dysregulation in children with ADHD [32]. By contrast, a reduction in left cerebellum gray matter in adults was associated with more severe emotional dysregulation and inattention [33].

Gao et al. [33] recently performed a meta-analysis of VBM that included 1051 patients with ADHD and 887 control patients. They confirmed reduction in gray matter volume in the anterior cingulate cortex (ACC), bilateral striatum, left perirolandic cortexes, right superior frontal cortex, left caudate, and orbitofrontal cortex.

VBM studies highlight frontal lobe structures, such as the ACC and orbitofrontal structures, as being altered in ADHD as well as the relation between emotional dysregulation and left frontal lobe changes in children but not adults, VBM studies are most useful in comparing two groups (i.e., ADHD vs typical development [TD]); the use of VBM to characterize individual patients therefore is not advised.

Diffusion Tensor Imaging

DTI studies report white matter variations in ADHD, similar to the focus on gray matter in volumetric studies. DTI findings are less uniform in children than in adults, perhaps because of superimposed myelination changes in the developing brain. For example, most of the variation identified in children with ADHD, such as lower volumes in isthmus and splenic parts of the corpus callosum, normalizes in adults [34].

Differences in fractional anisotropy (FA) have also been reported in the isthmus and splenium of the corpus callosum; the posterior mid parts of the corpus callosum also show significantly lower FA in ADHD [34].

In addition to the corpus callosum, the posterior corona radiata, longitudinal fasciculi, internal and external capsules, anterior thalamic radiations, right inferior frontooccipital fasciculus, and orbitofrontal tracts show reduced FA, differing by sex [35, 36]. For instance, patients with ADHD show bilateral reductions in FA within primary motor tracts compared with control patients, and girls with ADHD show higher FA bilaterally within medial orbitofrontal regions [35]. An age effect is reported for whole-brain and anterior thalamic FA, indicating more reductions in FA in children with ADHD than adults with ADHD [37–40].

DTI studies have also examined associations with the core hyperactivity/impulsivity symptoms of ADHD. Impulsivity is not associated with motor regions but is negatively correlated with FA of bilateral anterior and posterior corona radiata, right superior and left inferior longitudinal fasciculus, bilateral internal capsules, left external capsule, and corticospinal tracts [37, 41]. This inverse correlation (i.e., association of lower FA with greater symptoms) is consistent with measures of impulsivity in children without an ADHD diagnosis [37]. Although some studies argue that behavioral difficulties are caused by difficulties in motor inhibition, these studies contribute to the theory that both motor and reward circuitry are involved in ADHD.

In summary, DTI studies have largely focused on correlations between anisotropy measures and behavioral changes in ADHD. Sudre et al. [42] coined the term "developmental dysconnectome" to imply that anomalous connections lead to developmental disruption in ADHD. The work of Sudre and colleagues implicated the following white matter tracts as influential in the cognitive control and attention system of the brain: the right uncinate fasciculus (impulsivity), left cingulum (misbehavior and hypermotor activity), anterior thalamic radiations (motor activity and restlessness), right superior longitudinal fasciculus (working memory and attention), and various sections of the corpus callosum (cognitive) [42, 43]. These DTI studies included samples of 38–285 patients. Despite the group differences, individual patients may have disparate findings given the wide variability.

Functional Imaging Findings

Functional MRI—Various studies have suggested that fMRI findings can distinguish patients with ADHD from healthy control patients. Both resting-state fMRI (rsfMRI) (Fig. 2) and task-based fMRI studies have shown findings that differ among ADHD subtypes.

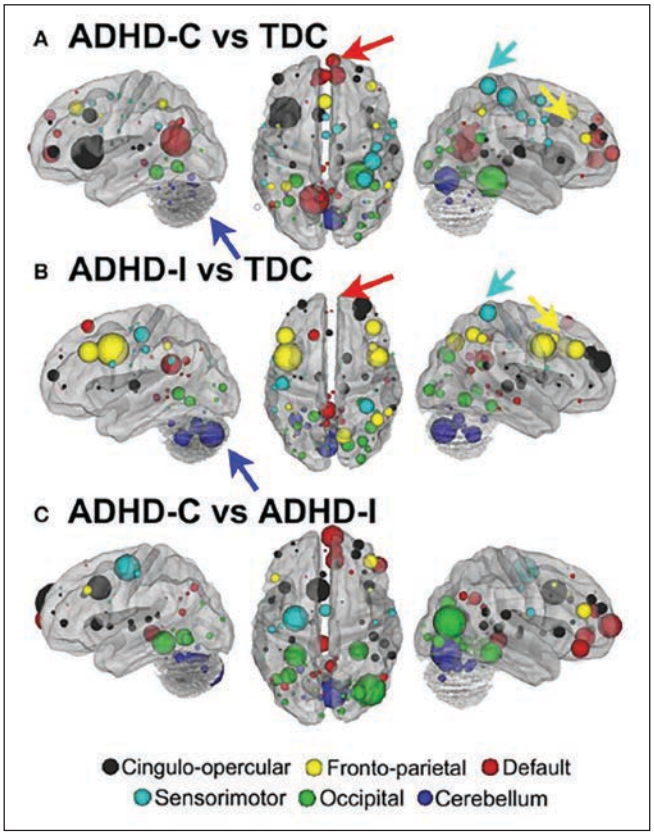


Fig. 2—Two most common subtypes of attention-deficit/hyperactivity disorder (ADHD) (predominantly inattentive ADHD [ADHD-I] and ADHD with combined presentation of both inattention and hyperactivity [ADHD-C]) show distributed patterns of atypical connectivity relative to typically developing children (TDC), as measured by node strength. Color of arrows matches color of circles in key that represent areas of anatomy. (Image reprinted and legend adapted from Fair DA, Nigg JT, Iyer S, et al., doi.org/10.3389/fnsys.2012.00080, © 2013 Fair DA, Nigg JT, Iyer S, Bathula D, Mills KL, Dosenbach NUF, Schlaggar BL, Mennes M, Gutman D, Bangaru S, Buitelaar JK, Dickstein DP, Di Martino A, Kennedy DN, Kelly C, Luna B, Schweitzer JB, Velanova K, Wang YF, Mostofsky S, Castellanos FX, Milham MP, subject to terms and including disclaimer in Section 5 of Creative Commons Attribution 3.0 Unported License, creativecommons.org/licenses/by/3.0/legalcode)
A, Node strength for ADHD-C versus TDC shows strong differentiation in regions of medial prefrontal cortex among other distributed systems.
B, Node strength for ADHD-I versus TDC shows differentiation distributed throughout cortex as well, with prominent nodes including bilateral, dorsolateral, prefrontal, and cerebellar regions among others.
C, Comparisons between subtypes ADHD-C and ADHD-I show similar trends. Node colors shown denote network categorization.

Task-based functional MRI—Using a flanker/no go fMRI task, Iannaccone et al. [44] found that when compared with control patients, adolescent patients with ADHD had larger clusters in the right insula and precuneus, middle cingulate gyrus, caudate, left thalamus, bilateral fusiform gyrus, posterior cingulate gyrus, lingual gyrus, middle temporal gyrus, superior temporal gyrus, cuneus, middle occipital gyrus, hippocampus, and parahippocampus. By contrast, control patients had more activation in the bilateral inferior frontal gyri, middle frontal gyrus, dorsolateral prefrontal gyrus, and superior frontal gyri. Activation in the dorsal ACC and insula are also important predictors of ADHD in preschool-age children [45]. Other studies have shown the relationship between ADHD severity and hypoactivity of the right nucleus accumbens in go/no go tasks as well as heightened age-related connectivity across several insula subregions [46–48].

In a study of adults with childhood-onset ADHD performing task-based stop (inhibitory function) and cognitive switch (attentional) paradigms, the patients with ADHD showed reduced activation in the bilateral inferior prefrontal cortex, caudate, and thalamus during both tasks as well as in the left parietal lobe during the switch task, when compared with control patients [49]. These findings matched those in children with ADHD, suggesting that functional disruptions persist into adulthood.

Other functional hyperactivities and hypoactivities are reported as key indicators of ADHD. Decreased blood flow to the frontostriatal and frontal regions, as well as the hypoactivity of the right nucleus accumbens and frontoparietal and frontostriatal regions during task-based studies of reward anticipation, have been reported [46, 49]. Mostofsky et al. [50] showed reduced contralateral motor cortex and right parietal cortex activation during both right-handed finger sequencing and left-handed finger sequencing.

A recent meta-analysis of 1914 patients with ADHD found little consensus among studies with task-based fMRI [51]. A consistent aberrant finding using neutral stimuli was noted in the left putamen, and activity was decreased in the left inferior frontal gyrus in male patients. The authors proposed that an abnormality in these parts may be associated with hyperactivity, impulsivity, disinhibition, and inattention symptoms of ADHD, because the dopamine-rich ventral putamen receives fibers from the inferior frontal gyrus [51]. Discrepancies between studies were attributed to heterogeneous samples of patients with ADHD, variable experimental designs and tasks, preprocessing variability, and nonuniform statistical tests.

Resting-state functional MRI—The use of rsfMRI studies in ADHD can eliminate concerns regarding attention and compliance during task-based fMRI studies. Degree centrality is an index of the number of nodes of connectivity at a voxel level. Reduced degree centrality indicates that information transfer is less efficient and slower. Reduced degree centrality was shown in 35 children with ADHD, affecting the right posterior cingulate gyrus, left medial superior frontal gyrus, right inferior parietal gyrus, right middle frontal gyrus, left superior frontal gyrus, right superior frontal gyrus, and bilateral rostral supplemental motor area [52, 53]. Rosch et al. [53] showed that in girls with ADHD, the "striatum is intrinsically more strongly connected to frontal regions, being both more functionally segregated (e.g., negatively correlated) with the anterior dorsolateral prefrontal cortex and more functionally integrated (e.g., positively correlated) with the ventromedial prefrontal cortex" [53]; there was weaker connectivity between the amygdala and the latter [53].

In a study of 247 children who were 3–6 years old, measures of executive function were associated with rsfMRI network findings as predictors of ADHD [45]. Worse executive function was associated with stronger positive connectivity between the dorsal anterior cingulate cortex and bilateral anterior insula and with stronger negative connectivity between the dorsal anterior cingulate cortex and dorsolateral prefrontal cortex of the posterior precuneus as well as between the insula hub seed region and the superior parietal region. Increased global connectivity was found in children prone to ADHD and the salience network [45].

Shappell et al. [54] recently examined rapid changes in dynamic rsfMRI connectivity, comparing children with ADHD and children with TD. Children with ADHD transfer in and out of various functional networks and the default mode network more rapidly than do control patients. Shappell and colleagues concluded that disrupted functional connectivity may explain concomitant symptoms of attentional and cognitive deficits [54]. The difficulty of parsing differences between children with ADHD, those with autism spectrum disorder, and those with comorbid autism spectrum disorder and ADHD was shown in another rsfMRI study that revealed no group differences in network functional connectivity across diagnoses and measures of executive function [55].

A recent meta-analysis that assessed rsfMRI reported significantly decreased synchrony within components in individuals with ADHD that would disrupt the interplay between the disrupted default mode network and the cognitive control network; no consistency in any abnormal interaction in the location of the components of the default mode network and cognitive control network was observed between studies. Also, disruption of connectivity in cognitive, reward, and effective cortico-striato-thalamo-cortical loops was noted, with both hyper- and hypoconnectivity reported [56].

Another meta-analysis [57] of the different subtypes of ADHD reported no significant subtype differences in gray matter volumes in most studies. However, two studies showed decreased volumes in regions associated with nodes of the default mode network, including the posterior cingulate, precuneus, and parahippocampal regions, in the ADHD-I group [58] in comparison with the ADHD-C group and a reduced hippocampal volume in the ADHD-C group versus the ADHD-I group [59]. Task-based fMRI studies evaluating these two subtypes showed both increased and decreased activation in frontoparietal regions in ADHD-I and in occipitoparietal regions in ADHD-C, depending on the functional task.

Another meta-analysis that involved the use of rsfMRI found changes in activation in the left superior temporal gyrus in children (not adults) who were receiving or not receiving medication [56]. However, a meta-analysis of rsfMRI studies of pharmacologic-induced changes in ADHD reported that methylphenidate treatment was associated with increased fractional amplitude of low-frequency fluctuations in precentral and postcentral gyri and lingual gyrus and decreased regional homogeneity in postcentral and lingual gyri, whereas contrasts of methylphenidate and atomoxetine showed opposite results with the same index (FA of low-frequency fluctuations) [60].

Overall, the task-based fMRI and rsfMRI studies suggest that many areas of the brain show hyper- and hypoactivities depending on the task. Hypoactivity has been observed in the accumbens nucleus and frontoparietal and frontostriatal regions, whereas hyperactivity has been observed in the basal ganglia and ACC. Experiments involving the use of rsfMRI have shown evidence of functional dysconnectivity compared with observations in children with TD across most networks, but none specifically. Caution is recommended in applying these conclusions to individual patients.

MR Spectroscopy

MRS has been used to investigate alterations in brain metabolism in ADHD. Results are inconsistent because of variation in the approaches, quantification methods, and patient samples as well as the natural heterogeneity of the disease.

Several studies reported no difference in MRS findings between children with ADHD and age-matched control patients in terms of *N*-acetylaspartate, choline compounds, and creatine and phosphocreatine measured from the right prefrontal cortex, left striatum, ACC, cerebellum, superior temporal gyrus, occipital lobe, and prefrontal cortex [61–65]. Other studies showed that creatine, in addition to choline and myo-inositol, is reduced in the middle frontal gyrus of patients with ADHD [66].

Studies assessing glutamine, glutamate, and γ-aminobutyric acid (GABA) have yielded stronger changes in ADHD. Increased frontal-striatal glutamate, glutamine, and GABA levels [63], increased striatal creatine levels [61], and reduced striatal GABA levels in children with ADHD [62] have been reported (Fig. 3). A study performed at 7 T showed significant reduction in the GABA-to-creatine ratio in the corpus striatum of children with ADHD, with significant positive correlation to measures of impaired behavioral inhibitory control [62]. Medication may affect these measures, because GABA levels differed between those with and without chronic stimulant use [67].

MRS findings have also been assessed with respect to the clinical presentation of ADHD. Patients with worse attention, concentration, and set-shifting have lower creatine signal in the lower right middle frontal cortex [66].

Because studies have shown that the sex and age are important covariates for creatine, choline, membrane phospholipid, glutamate, and glutamine, special considerations are needed for age and sex matching in MRS research studies [68, 69].

In conclusion, the MRS findings in patients with ADHD are debated. However, glutamatergic and creatine signals appear to be increased in the frontal-striatal regions, GABAergic differences may also be observed in regions associated with corticostriatal function, and membrane phospholipids and their precursors may also be reduced in the basal ganglia and increased in inferior parietal regions. Age and sex are important covariates that should be controlled in any MRS ADHD study.

PET

Most PET studies have evaluated the effects of pharmaceutical agents on patients with ADHD. However, PET has also been used to study certain molecules, such as norepinephrine, dopamine, and serotonin, in drug-naive patients.

Studies have suggested that norepinephrine transporter availability is reduced in fronto-parietal-thalamic-cerebellar regions. However, the norepinephrine concentrations or distributions are not associated with the severity of behavioral abnormalities in ADHD [70, 71].

Dopamine, dopamine receptor-1 (D1R), and dopamine transporters (DATs) have been evaluated in the most depth. Wiers et al. [72] showed a negative correlation between D1R and DAT1 promoter methylation in ADHD. A decrease in D1R has been measured in the ACC and is significantly associated with severe hyperactivity. Similar reductions are reported in the prefrontal cortex region, especially in the medial and left prefrontal areas [73, 74]. Moreover, a task-based study on dopamine showed increased phasic dopamine release and decreased tonic release in the right caudate [75]. In addition to the increase in dopamine in ADHD, PET also shows increased microglia activation in the dorsolateral prefrontal cortex and orbitofrontal cortex. Hyperactivation is associated with more severe deficit in processing speed and attention. Higher microglia activation is associated with lower dopamine neurotransmitter activity [74].

These studies cumulatively suggest alterations in the cortical and deep gray dopamine system in ADHD. DAT imaging is the current focus of PET studies because the therapeutic benefits of methylphenidate, which targets DAT, are well known. The focus of these dopaminergic imaging studies has been the caudate nucleus (DAT) and ACC (decrease in D1R). Microglial activation in the dorsolateral prefrontal cortex and orbitofrontal cortex has recently been implicated in inattention.

Artificial Intelligence Modeling

AI modeling has been applied to nearly all modalities for structural and functional imaging of the brain in ADHD. One model, trained to focus on whole brain volume and regional cortical thicknesses, noted the best accuracy when weighting reduced volumes in the inferior frontal cortex, bilateral sensorimotor cortex, and insula. These AI findings yielded 85.1% accuracy in differentiating children with ADHD and healthy patients [76]. A similar AI analysis by Sun et al. [77] included shape changes in the left temporal lobe, bilateral cuneus thickness, and FA values in the left cerebral peduncle in the model, yielding accuracy of 73.7%. Another study showed the best classifiers to be the ventrolateral cortex, limbic regions, and insula volume [78].

VBM studies have also been used to train AI models. The model by Gehricke et al. [22] reached 83% accuracy in differentiating patients with ADHD and healthy control patients when focusing on structural shape changes of the middle and superior temporal gyrus, frontobasal portions of both frontal lobes, left caudate head volume, and the DTI parameters of the superior longitudinal fasciculus and corticolimbic circuits [22]. DTI AI models have reported accuracies of 83–90% [79] with the use of whole-brain functional connectivity. However, these asymmetries diminish with stimulant therapy and age in patients with ADHD [22, 39, 41].

A machine learning competition using a combined database (the ADHD-200 Global Competition database) was convened to derive AI classification tools for ADHD using pooled structural and functional MRI data. Eloyan et al. [80] won the competition with a program showing 61% accuracy, 94% specificity, and 21% sensitivity in classifying brains into the TD, ADHD-I, or ADHD-C categories. However, Deshpande et al. [79] achieved 90% accuracy in differentiating children with ADHD and those with TD as well as approximately 95%

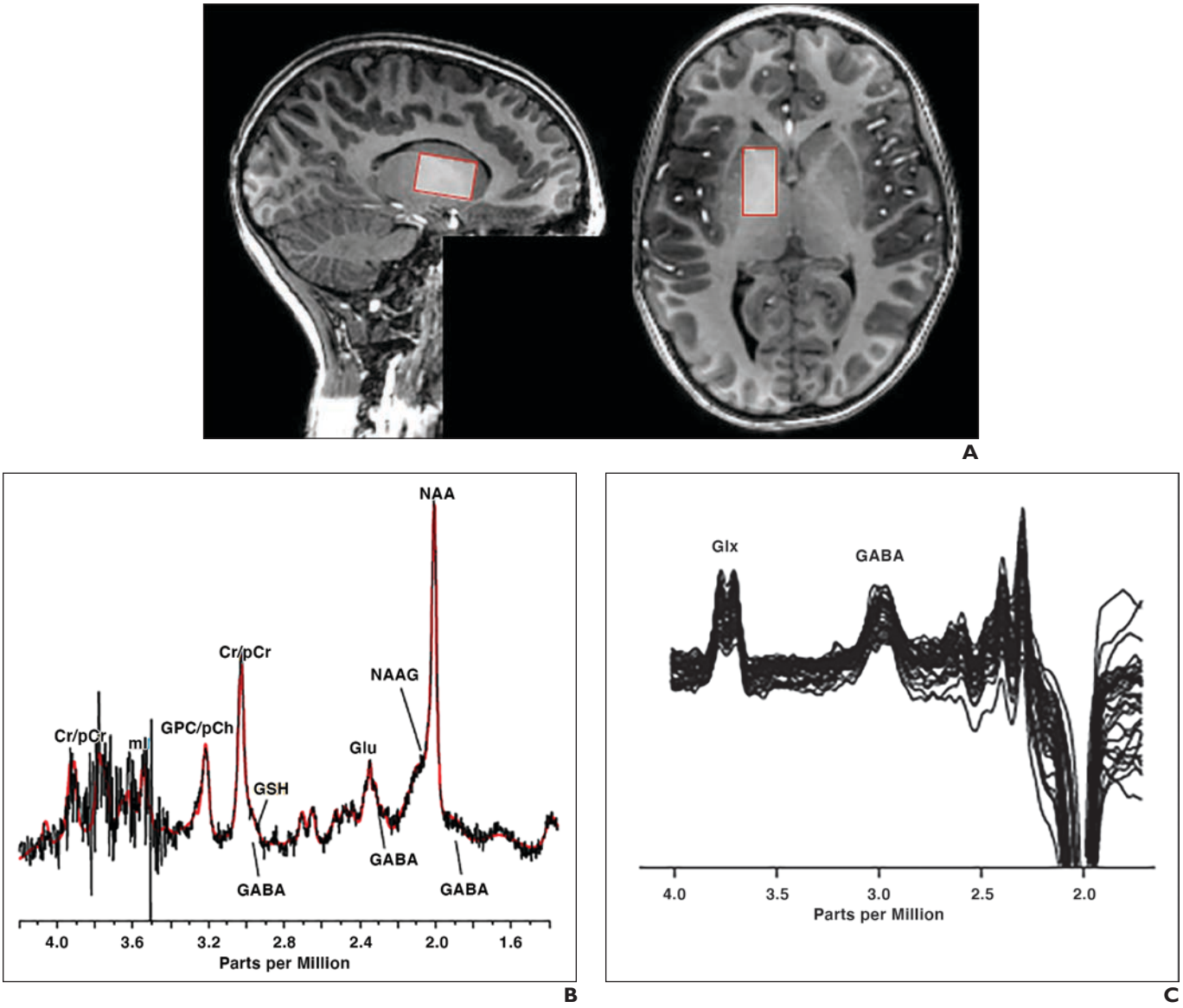


Fig. 3—MR spectroscopy (MRS) examination of neurochemistry of attention-deficit/hyperactivity disorder (ADHD), with specific focus on main inhibitory and excitatory neurotransmitters γ-aminobutyric acid (GABA) and glutamate (Glu).
A, 6-year-old boy with ADHD who underwent MRS performed at 7 T. Single-voxel MRS examined these metabolites in predefined ROIs (*red rectangles*), as indicated by example of voxel placed over striatum (as shown on sagittal image [*left*] and axial image [*right*]), which serves important role in motor planning and coordination and is affected in ADHD.
B, Example of spectrum from voxel shown in **A**. Ultra-high-field MRI has benefit of high signal-to-noise ratio, allowing shorter acquisitions and smaller (i.e., more specific) voxels. In this spectrum, GABA and Glu can be identified and quantified. Other major peaks, such as *N*-acetyl cysteine (NAA), *N*-acetylaspartylglutamic acid (NAAG), creatine and phosphocreatine (Cr/pCr), glycerylphosphorylcholine and phosphocholine (GPC/pCh), glutathione (GSH), and mI (myo-inositol), can also be identified. Metabolites are typically expressed as millimolar or as ratios. Red areas show fit of spectrum. Reduced striatal GABA has been observed on MRS performed at 7 T in children with ADHD [62].
C, Alternatively, GABA can be detected using J-difference editing, modulating metabolite of interest to remove unwanted signals (NAA, creatinine, and choline) from spectrum. Example of GABA-edited MRS examination, performed at 3 T, of 9-year-old boy who participated in cohort study that showed aberrant association with measures of inhibition in children with ADHD [91]. Previous study had shown that sensorimotor GABA levels are reduced in children with ADHD [92]. Combination of glutamate and glutamine (Glx) is also resolved using spectral editing.

accuracy in determining disease subtype when a fully connected cascade artificial neural network was applied using 3-T rsfMRI data from 190 brain regions of 744 patients with TD, 240 patients with ADHD-C, and 173 patients with ADHD-I in the ADHD-200 Global Competition database. The features that were most important for AI classification were inputs to the left orbitofrontal region (higher in ADHD) and the vermis of the cerebellum (higher in TD) [79]. Another study [81] achieved a high classification accuracy by using demographic or phenotypic characteristics of patients rather than any imaging-based classifiers (62.5%). Combining phenotypic and functional imaging data achieves nominally better accuracy (65%) [82].

Considering the nature of the disease, multimodal data, and changes that are below the threshold of visual perception during routine imaging analysis, AI techniques may take a central stage in consolidating

ADHD research. We believe that as imaging data from more homogeneous populations of patients with ADHD are provided to machine learning algorithms, AI methods will allow distinction between normal variation misbehavior and ADHD, categorization of ADHD subtypes, differentiation of patients with ADHD from those with other neurobehavioral disorders, and detection of combined disorders.

Imaging During Therapy

A variety of modalities have been used to assess the effect of drugs for treating patients with ADHD, not only on the basis of clinical outcomes but also with the use of neuroimaging techniques. Anatomic studies, even those with larger sample sizes (1713 patients with ADHD and 1529 control patients) failed to recognize any association of medication state or clinical symptoms scores with the volumes of accumbens, amygdala, caudate, hippocampus, putamen, and whole brain [19]. One study found increased FA in the left corpus callosum of boys who were receiving methylphenidate treatment [83].

As previously noted, a decrease in the dopamine level in the striatum is a main alteration in ADHD. As expected, drugs such as methylphenidate lead to increases in dopamine uptake on PET in these sites [84].

Iron hemostasis in the brain correlates with dopamine levels. The iron load of medication-naive children with ADHD is lower than that in healthy patients. However, the iron level in the globus pallidus, putamen, caudate nucleus, and thalamus improves with psychostimulant treatment [85].

Methylphenidate therapy in ADHD leads to the observation of various alterations in MRS studies. A 2-month methylphenidate-only regimen led to increases in the glutamate plus glutamine and glutamate plus glutamine-to-creatine ratio of left white matter [86]. By contrast, studies showed no alteration in glutamate and glutamine, *N*-acetylaspartate, choline, or myo-inositol from methylphenidate [87, 88]. This observation may be explained by MRS and genetics studies showing that those with weak or no response to methylphenidate have polymorphisms in their *DAT1* gene, which may neutralize the effect of the drug [89]. Atomoxetine therapy also increases the ratio of *N*-acetylaspartate– and *N*-acetylaspartate to creatine in the left dorsolateral prefrontal cortex and decreases the choline-to-creatine ratio in the right dorsolateral prefrontal cortex [86].

PET studies of regional cerebral blood flow have also been performed for patients who did not receive treatment and those who received methylphenidate treatment for 3 weeks. The results showed increased regional cerebral blood flow in the precentral gyri, left caudate nucleus, and right claustrum of patients who did not receive treatment compared with those who did receive treatment. However, blood flow increases in the cerebellar vermis, which is known as the planning and execution region of the motor system, could be identified after patients had received methylphenidate therapy for 3 weeks [90].

In summary, methylphenidate therapy, which is widely used for ADHD, has effects that are most notable on PET but can affect DTI measures, MRS metabolites, and iron levels measurable in the brain.

Future Research

Despite years of study and multimodal approaches, the anatomic and pathophysiologic bases of childhood and adult ADHD are not well understood. This likely reflects the nature of ADHD: the disorder is multifactorial with heterogeneous phenotypes and genotypes such that imaging studies are not definitive unless they include large samples to stratify the disorder. In addition, the results of imaging studies are mitigated by the impact of age, sex, medications, and cognitive therapies used to reduce symptoms.

Furthermore, the anatomic variability of the developing brain from childhood to adolescence to adulthood may obfuscate detection of an anatomic site that can be directly implicated in ADHD. Nonetheless, a comprehensive imaging protocol that combines gray and white matter volumetry, DTI tractography, MRS, and rsfMRI sequences in medication-naive children and adults with ADHD would greatly benefit understanding this disorder. These anatomic and functional datasets in patients and age-matched control patients should be subjected to AI algorithms to better localize the regions most "at fault" in ADHD. If only one technique can be applied to a research protocol, we advocate for the use of rsfMRI because it requires less patient cooperation, can address the connectivity issues that underlie the disorder, and can be easily implemented in group and individual datasets. Scanning times are also acceptable.

Because the phenotype of ADHD manifestations varies by age, we believe that future studies should be longitudinal, with clusters of patients evaluated at 5-year intervals (i.e., at 0–5, 6–10, 11–15, and 16–20 years), to observe dynamic changes. A follow-up study of successfully treated patients from the original cohort would then help examine whether changes occurred in suspected locations and functions

The growing incidence of ADHD in the general population, the reasons for which are unclear, requires that the neuroradiology community provide greater resources and more focused attention for studying this illness. The impacts on individuals, family members, caregivers, and society as a whole suggest that resource investment by neuroscientists in understanding the disease will be worthwhile.

References

1. Magnin E, Maurs C. Attention-deficit/hyperactivity disorder during adulthood. *Rev Neurol (Paris)* 2017; 173:506–515
2. Wilens TE, Morrison NR, Prince J. An update on the pharmacotherapy of attention-deficit/hyperactivity disorder in adults. *Expert Rev Neurother* 2011; 11:1443–1465
3. Davies W. Sex differences in attention deficit hyperactivity disorder: candidate genetic and endocrine mechanisms. *Front Neuroendocrinol* 2014; 35:331–346
4. Gallo EF, Posner J. Moving towards causality in attention-deficit hyperactivity disorder: overview of neural and genetic mechanisms. *Lancet Psychiatry* 2016; 3:555–567
5. Substance Abuse and Mental Health Services Administration. *DSM-5 changes: implications for child serious emotional disturbance.* Substance Abuse and Mental Health Services Administration, 2016
6. Klein RG, Mannuzza S, Olazagasti MA, et al. Clinical and functional outcome of childhood attention-deficit/hyperactivity disorder 33 years later. *Arch Gen Psychiatry* 2012; 69:1295–1303
7. Noordermeer SD, Luman M, Oosterlaan J. A systematic review and meta-analysis of neuroimaging in oppositional defiant disorder (ODD) and conduct disorder (CD) taking attention-deficit hyperactivity disorder (ADHD) into account. *Neuropsychol Rev* 2016; 26:44–72

8. Mannuzza S, Klein RG. Long-term prognosis in attention-deficit/hyperactivity disorder. *Child Adolesc Psychiatr Clin N Am* 2000; 9:711–726
9. Ahnemark E, Di Schiena M, Fredman AC, Medin E, Söderling JK, Ginsberg Y. Health-related quality of life and burden of illness in adults with newly diagnosed attention-deficit/hyperactivity disorder in Sweden. *BMC Psychiatry* 2018; 18:223
10. Nylander L, Holmqvist M, Gustafson L, Gillberg C. Attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) in adult psychiatry: a 20-year register study. *Nord J Psychiatry* 2013; 67:344–350
11. Park MTM, Raznahan A, Shaw P, Gogtay N, Lerch JP, Chakravarty MM. Neuroanatomical phenotypes in mental illness: identifying convergent and divergent cortical phenotypes across autism, ADHD and schizophrenia. *J Psychiatry Neurosci* 2018; 43:201–212
12. Albajara Sáenz A, Villemonteix T, Massat I. Structural and functional neuroimaging in attention-deficit/hyperactivity disorder. *Dev Med Child Neurol* 2019; 61:399–405
13. Mostofsky SH, Cooper KL, Kates WR, Denckla MB, Kaufmann WE. Smaller prefrontal and premotor volumes in boys with attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2002; 52:785–794
14. Lu L, Zhang L, Tang S, et al. Characterization of cortical and subcortical abnormalities in drug-naive boys with attention-deficit/hyperactivity disorder. *J Affect Disord* 2019; 250:397–403
15. Wu ZM, Llera A, Hoogman M, et al. Linked anatomical and functional brain alterations in children with attention-deficit/hyperactivity disorder. *Neuroimage Clin* 2019; 23:101851
16. Klein M, Souza-Duran FL, Menezes AKPM, Alves TM, Busatto G, Louzã MR. Gray matter volume in elderly adults with ADHD: associations of symptoms and comorbidities with brain structures. *J Atten Disord* 2021; 25:829–838
17. Filipek PA, Semrud-Clikeman M, Steingard RJ, Renshaw PF, Kennedy DN, Biederman J. Volumetric MRI analysis comparing subjects having attention-deficit hyperactivity disorder with normal controls. *Neurology* 1997; 48:589–601
18. Liu Q, Chen L, Li F, et al. Voxel-based morphometry in medicated-naive boys with attention-deficit/hyperactivity disorder (ADHD) [in Chinese]. *Sheng Wu Yi Xue Gong Cheng Xue Za Zhi* 2016; 33:526–532
19. Hoogman M, Bralten J, Hibar DP, et al. Subcortical brain volume differences in participants with attention deficit hyperactivity disorder in children and adults: a cross-sectional mega-analysis. *Lancet Psychiatry* 2017; 4:310–319
20. Castellanos FX, Giedd JN, Marsh WL, et al. Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. *Arch Gen Psychiatry* 1996; 53:607–616
21. Dang LC, Samanez-Larkin GR, Young JS, Cowan RL, Kessler RM, Zald DH. Caudate asymmetry is related to attentional impulsivity and an objective measure of ADHD-like attentional problems in healthy adults. *Brain Struct Funct* 2016; 221:277–286
22. Gehricke JG, Kruggel F, Thampipop T, et al. The brain anatomy of attention-deficit/hyperactivity disorder in young adults: a magnetic resonance imaging study. *PLoS One* 2017; 12:e0175433
23. Ambrosino S, de Zeeuw P, Wierenga LM, van Dijk S, Durston S. What can cortical development in attention-deficit/hyperactivity disorder teach us about the early developmental mechanisms involved? *Cereb Cortex* 2017; 27:4624–4634
24. Noordermeer SDS, Luman M, Greven CU, et al. Structural brain abnormalities of attention-deficit/hyperactivity disorder with oppositional defiant disorder. *Biol Psychiatry* 2017; 82:642–650
25. Kibby MY, Dyer SM, Lee SE, Stacy M. Frontal volume as a potential source of the comorbidity between attention-deficit/hyperactivity disorder and reading disorders. *Behav Brain Res* 2020; 381:112382
26. Van Dessel J, Sonuga-Barke E, Moerkerke M, et al. The amygdala in adolescents with attention-deficit/hyperactivity disorder: structural and functional correlates of delay aversion. *World J Biol Psychiatry* 2020; 21:673–684
27. Hoogman M, Muetzel R, Guimaraes JP, et al. Brain imaging of the cortex in ADHD: a coordinated analysis of large-scale clinical and population-based samples. *Am J Psychiatry* 2019; 176:531–542
28. Hynd GW, Hern KL, Novey ES, et al. Attention deficit-hyperactivity disorder and asymmetry of the caudate nucleus. *J Child Neurol* 1993; 8:339–347
29. Schrimsher GW, Billingsley RL, Jackson EF, Moore BD 3rd. Caudate nucleus volume asymmetry predicts attention-deficit hyperactivity disorder (ADHD) symptomatology in children. *J Child Neurol* 2002; 17:877–884
30. Uhlíkova P, Paclt I, Vaneckova M, et al. Asymmetry of basal ganglia in children with attention deficit hyperactivity disorder. *Neuroendocrinol Lett* 2007; 28:604–609
31. Postema MC, et al. Analysis of structural brain asymmetries in attention-deficit/hyperactivity disorder in 39 datasets. bioRxiv website. www.biorxiv.org/content/10.1101/2020.03.03.974758v1. Published March 5, 2020. Accessed March 28, 2021
32. Tsai CJ, Lin HY, Tseng IWY, Gau SSF. Brain voxel-based morphometry correlates of emotion dysregulation in attention-deficit hyperactivity disorder. *Brain Imaging Behav* 2021; 15:1388–1402
33. Gao X, Zhang M, Yang Z, et al. structural and functional brain abnormalities in Internet gaming disorder and attention-deficit/hyperactivity disorder: a comparative meta-analysis. *Front Psychiatry* 2021; 12:679437
34. Dramsdahl M, Westerhausen R, Haavik J, Hugdahl K, Plessen KJ. Adults with attention-deficit/hyperactivity disorder: a diffusion-tensor imaging study of the corpus callosum. *Psychiatry Res* 2012; 201:168–173
35. Jacobson LA, Peterson DJ, Rosch KS, Crocetti D, Mori S, Mostofsky SH. Sex-based dissociation of white matter microstructure in children with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2015; 54:938–946
36. Tamm L, Barnea-Goraly N, Reiss AL. Diffusion tensor imaging reveals white matter abnormalities in attention-deficit/hyperactivity disorder. *Psychiatry Res* 2012; 202:150–154
37. Aoki Y, Yoncheva YN, Chen B, et al. Association of white matter structure with autism spectrum disorder and attention deficit/hyperactivity disorder. *JAMA Psychiatry* 2017; 74:1120–1128
38. McNally MA, Crocetti D, Mahone EM, Denckla MB, Suskauer SJ, Mostofsky SH. Corpus callosum segment circumference is associated with response control in children with attention-deficit hyperactivity disorder (ADHD). *J Child Neurol* 2010; 25:453–462
39. Douglas PK, Gutman B, Anderson A, et al. Hemispheric brain asymmetry differences in youths with attention-deficit/hyperactivity disorder. *Neuroimage Clin* 2018; 18:744–752
40. Nagel BJ, Bathula D, Herting M, et al. Altered white matter microstructure in children with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2011; 50:283–292
41. Aoki Y, Cortese S, Castellanos FX. Research Review: Diffusion tensor imaging studies of attention-deficit/hyperactivity disorder: meta-analyses and reflections on head motion. *J Child Psychol Psychiatry* 2018; 59:193–202
42. Sudre G, Frederick J, Sharp W, et al. Mapping associations between polygenic risks for childhood neuropsychiatric disorders, symptoms of attention deficit hyperactivity disorder, cognition, and the brain. *Mol Psychiatry* 2020; 25:2482–2492
43. Chiang HL, Chen YJ, Shang CY, Tseng WY, Gau SS. Different neural substrates for executive functions in youths with ADHD: a diffusion spectrum imaging tractography study. *Psychol Med* 2016; 46:1225–1238
44. Iannaccone R, Hauser TU, Ball J, Brandeis D, Walitza S, Brem S. Classifying

adolescent attention-deficit/hyperactivity disorder (ADHD) based on functional and structural imaging. *Eur Child Adolesc Psychiatry* 2015; 24:1279–1289

45. Hawkey EJ, Tillman R, Luby JL, Barch DM. Preschool executive function predicts childhood resting-state functional connectivity and attention-deficit/hyperactivity disorder and depression. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2018; 3:927–936
46. Rasmussen J, Casey BJ, van Erp TG, et al.; MTA Neuroimaging Group. ADHD and cannabis use in young adults examined using fMRI of a Go/NoGo task. *Brain Imaging Behav* 2016; 10:761–771
47. Akkermans SEA, van Rooij D, Naaijen J, et al. Neural reward processing in paediatric Tourette syndrome and/or attention-deficit/hyperactivity disorder. *Psychiatry Res Neuroimaging* 2019; 292:13–22
48. Barber AD, Sarpal DK, John M, et al.; Pediatric Imaging, Neurocognition, and Genetics (PING) Study Consortium. Age-normative pathways of striatal connectivity related to clinical symptoms in the general population. *Biol Psychiatry* 2019; 85:966–976
49. Cubillo A, Halari R, Ecker C, Giampietro V, Taylor E, Rubia K. Reduced activation and inter-regional functional connectivity of fronto-striatal networks in adults with childhood attention-deficit hyperactivity disorder (ADHD) and persisting symptoms during tasks of motor inhibition and cognitive switching. *J Psychiatr Res* 2010; 44:629–639
50. Mostofsky SH, Rimrodt SL, Schafer JG, et al. Atypical motor and sensory cortex activation in attention-deficit/hyperactivity disorder: a functional magnetic resonance imaging study of simple sequential finger tapping. *Biol Psychiatry* 2006; 59:48–56
51. Samea F, Soluki S, Nejati V, et al. Brain alterations in children/adolescents with ADHD revisited: a neuroimaging meta-analysis of 96 structural and functional studies. *Neurosci Biobehav Rev* 2019; 100:1–8
52. Jiang K, Yi Y, Li L, et al. Functional network connectivity changes in children with attention-deficit hyperactivity disorder: a resting-state fMRI study. *Int J Dev Neurosci* 2019; 78:1–6
53. Rosch KS, Mostofsky SH, Nebel MB. ADHD-related sex differences in fronto-subcortical intrinsic functional connectivity and associations with delay discounting. *J Neurodev Disord* 2018; 10:34
54. Shappell HM, Duffy KA, Rosch KS, et al. Children with attention-deficit/hyperactivity disorder spend more time in hyperconnected network states and less time in segregated network states as revealed by dynamic connectivity analysis. *Neuroimage* 2021; 229:117753
55. Dajani DR, Burrows CA, Odriozola P, et al. Investigating functional brain network integrity using a traditional and novel categorical scheme for neurodevelopmental disorders. *Neuroimage Clin* 2019; 21:101678
56. Cortese S, Aoki YY, Itahashi T, Castellanos FX, Eickhoff SB. Systematic review and meta-analysis: resting-state functional magnetic resonance imaging studies of attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2021; 60:61–75
57. Saad JF, Griffiths KR, Korgaonkar MS. A systematic review of imaging studies in the combined and inattentive subtypes of attention deficit hyperactivity disorder. *Front Integr Nuerosci* 2020; 14:31
58. Anderson A, Douglas PK, Kerr WT, et al. Non-negative matrix factorization of multimodal MRI, fMRI and phenotypic data reveals differential changes in default mode subnetworks in ADHD. *Neuroimage* 2014; 102:207–219
59. Al-Amin M, Zinchenko A, Geyer T. Hippocampal subfield volume changes in subtypes of attention deficit hyperactivity disorder. *Brain Res* 2018; 1685:1–8
60. Pereira-Sanchez V, Franco AR, Vieira D, et al. Systematic review: medication effects on brain intrinsic functional connectivity in patients with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2021; 60:222–235
61. Carrey NJ, MacMaster FP, Gaudet L, Schmidt MH. Striatal creatine and glutamate/glutamine in attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol* 2007; 17:11–17
62. Puts NA, Ryan M, Oeltzschner G, Horska A, Edden RAE, Mahone EM. Reduced striatal GABA in unmedicated children with ADHD at 7T. *Psychiatry Res Neuroimaging* 2020; 301:111082
63. MacMaster FP, Carrey N, Sparkes S, Kusumakar V. Proton spectroscopy in medication-free pediatric attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2003; 53:184–187
64. Naaijen J, Forde NJ, Lythgoe DJ, et al. Fronto-striatal glutamate in children with Tourette's disorder and attention-deficit/hyperactivity disorder. *Neuroimage Clin* 2016; 13:16–23
65. Endres D, Perlov E, Maier S, et al. Normal neurochemistry in the prefrontal and cerebellar brain of adults with attention-deficit hyperactivity disorder. *Front Behav Neurosci* 2015; 9:242
66. Tafazoli S, O'Neill J, Bejjani A, et al. ^{1}H MRSI of middle frontal gyrus in pediatric ADHD. *J Psychiatr Res* 2013; 47:505–512
67. Solleveld MM, Schrantee A, Puts NAJ, Reneman L, Lucassen PJ. Age-dependent, lasting effects of methylphenidate on the GABAergic system of ADHD patients. *Neuroimage Clin* 2017; 15:812–818
68. Stanley JA, Kipp H, Greisenegger E, et al. Evidence of developmental alterations in cortical and subcortical regions of children with attention-deficit/hyperactivity disorder: a multivoxel in vivo phosphorus 31 spectroscopy study. *Arch Gen Psychiatry* 2008; 65:1419–1428
69. Endres D, Tebartz van Elst L, Maier SJ, et al. Neurochemical sex differences in adult ADHD patients: an MRS study. *Biol Sex Differ* 2019; 10:50
70. Vanicek T, Spies M, Rami-Mark C, et al. The norepinephrine transporter in attention-deficit/hyperactivity disorder investigated with positron emission tomography. *JAMA Psychiatry* 2014; 71:1340–1349
71. Ulke C, Rullmann M, Huang J, et al. Adult attention-deficit/hyperactivity disorder is associated with reduced norepinephrine transporter availability in right attention networks: a (S,S)-O-[^{11}C]methylreboxetine positron emission tomography study. *Transl Psychiatry* 2019; 9:301
72. Wiers CE, Lohoff FW, Lee J, et al. Methylation of the dopamine transporter gene in blood is associated with striatal dopamine transporter availability in ADHD: a preliminary study. *Eur J Neurosci* 2018; 48:1884–1895
73. Ernst M, Zametkin AJ, Matochik JA, Jons PH, Cohen RM. DOPA decarboxylase activity in attention deficit hyperactivity disorder adults: a [fluorine-18]fluorodopa positron emission tomographic study. *J Neurosci* 1998; 18:5901–5907
74. Yokokura M, Takebasashi K, Takao A, et al. In vivo imaging of dopamine D1 receptor and activated microglia in attention-deficit/hyperactivity disorder: a positron emission tomography study. *Mol Psychiatry* 2020 May 21 [published online]
75. Badgaiyan RD, Sinha S, Sajjad M, Wack DS. Attenuated tonic and enhanced phasic release of dopamine in attention deficit hyperactivity disorder. *PLoS One* 2015; 10:e0137326
76. Yoo JH, Kim JI, Kim BN, Jeong B. Exploring characteristic features of attention-deficit/hyperactivity disorder: findings from multi-modal MRI and candidate genetic data. *Brain Imaging Behav* 2020; 14:2132–2147
77. Sun H, Chen Y, Huang Q, et al. Psychoradiologic utility of MR imaging for diagnosis of attention deficit hyperactivity disorder: a radiomics analysis. *Radiology* 2018; 287:620–630
78. Lim L, Marquand A, Cubillo AA, et al. Disorder-specific predictive classification of adolescents with attention deficit hyperactivity disorder (ADHD) relative to autism using structural magnetic resonance imaging. *PLoS One* 2013; 8:e63660

79. Deshpande G, Wang P, Rangaprakash D, Wilamowski B. Fully connected cascade artificial neural network architecture for attention deficit hyperactivity disorder classification from functional magnetic resonance imaging data. *IEEE Trans Cybern* 2015; 45:2668–2679
80. Eloyan A, Muschelli J, Nebel MB, et al. Automated diagnoses of attention deficit hyperactive disorder using magnetic resonance imaging. *Front Syst Neurosci* 2012; 6:61
81. Brown MR, Sidhu GS, Greiner R, et al. ADHD-200 Global Competition: diagnosing ADHD using personal characteristic data can outperform resting state fMRI measurements. *Front Syst Neurosci* 2012; 6:69
82. Ghiassian S, Greiner R, Jin P, Brown MR. Using functional or structural magnetic resonance images and personal characteristic data to identify ADHD and autism. *PLoS One* 2016; 11:e0166934
83. Bouziane C, Filatova OG, Schrantee A, Caan MWA, Vos FM, Reneman L. White matter by dffusion MRI following methylphenidate treatment: a randomized control trial in males with attention-deficit/hyperactivity disorder. *Radiology* 2019; 293:186–192
84. Birn RM, Converse AK, Rajala AZ, et al. Changes in endogenous dopamine induced by methylphenidate predict functional connectivity in nonhuman primates. *J Neurosci* 2019; 39:1436–1444
85. Adisetiyo V, Gray KM, Jensen JH, Helpern JA. Brain iron levels in attention-deficit/hyperactivity disorder normalize as a function of psychostimulant treatment duration. *Neuroimage Clin* 2019; 24:101993
86. Husarova V, Bittsansky M, Ondrejka I, Dobrota D. Prefrontal grey and white matter neurometabolite changes after atomoxetine and methylphenidate in children with attention deficit/hyperactivity disorder: a (1)H magnetic resonance spectroscopy study. *Psychiatry Res* 2014; 222:75–83
87. Maier S, Tebartz van Elst L, Philipsen A, et al. Effects of 12-week methylphenidate treatment on neurometabolism in adult patients with ADHD: the first double-blind placebo-controlled MR spectroscopy study. *J Clin Med* 2020; 9:2601
88. Jin Z, Zang YF, Zeng YW, Zhang L, Wang YF. Striatal neuronal loss or dysfunction and choline rise in children with attention-deficit hyperactivity disorder: a ^{1}H-magnetic resonance spectroscopy study. *Neurosci Lett* 2001; 315:45–48
89. Krause J. SPECT and PET of the dopamine transporter in attention-deficit/hyperactivity disorder. *Expert Rev Neurother* 2008; 8:611–625
90. Schweitzer JB, Lee DO, Hanford RB, et al. A positron emission tomography study of methylphenidate in adults with ADHD: alterations in resting blood flow and predicting treatment response. *Neuropsychopharmacology* 2003; 28:967–973
91. Harris AD, Gilbert DL, Horn PS, et al. Relationship between GABA levels and task-dependent cortical excitability in children with attention-deficit/hyperactivity disorder. *Clin Neurophysiol* 2021; 132:1163–1172
92. Edden RA, Crocetti D, Zhu H, Gilbert DL, Mostofsky SH. Reduced GABA concentration in attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 2012; 69:750–753
93. Reynolds CR, Kamphaus RW. Attention-deficit/hyperactivity disorder (ADHD). Pearson Assessments website. downloads.pearsonassessments.com/images/assets/basc-3/basc3resources/DSM5_DiagnosticCriteria_ADHD.pdf. Published 2013. Accessed August 9, 2021
94. [No authors listed]. Attention-deficit/hyperactivity disorder (ADHD). Cleveland Clinic website. my.clevelandclinic.org/health/diseases/4784-attention-deficithyperactivity-disorder-adhd. Reviewed January 12, 2021. Accessed August 4, 2021