# Brain abnormalities in attention-deficit hyperactivity disorder: a review

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**Aim.** To review the magnetic resonance imaging findings in child and adult attention-deficit hyperactivity disorder (ADHD).

**Development.** Studies have shown that ADHD is characterised by multiple functional and structural neural network abnormalities including most prominently fronto-striatal, but also fronto-parieto-temporal, fronto-cerebellar and even fronto-limbic networks. Evidence from longitudinal structural imaging studies has shown that ADHD is characterised by a delay in structural brain maturation. This is reinforced by indirect evidence from cross-sectional imaging studies for more immature brain function as well as structural and functional connectivity patterns, which, however, needs corroboration by longitudinal studies. Dysfunction of the ventrolateral prefrontal cortex seems to be more pronounced in ADHD relative to other pediatric disorders and there is some evidence for differential abnormalities in the basal ganglia. A meta-analysis of stimulant effects on brain function shows that the most consistent mechanism of action of acute psychostimulant medication is the increased activation of the inferior prefrontal cortex and the basal ganglia. First attempts to use neuroimaging data to make individual diagnostic classifications of ADHD children based on pattern recognition techniques are promising but need replication across centres and scanners.

**Conclusions.** The last two decades of neuroimaging have shaped out biomarkers of ADHD. Future studies will need to focus on using this information for clinical translation such as using neuroimaging for individual diagnostic and prognostic classification or by using neuroimaging as a neurotherapy to reverse those brain function abnormalities that have been established over the last two decades of neuroimaging.

**Key words.** Atomoxetine. Attention-deficit hyperactivity disorder (ADHD). Diffusion tensor imaging (DTI). Functional magnetic resonance imaging (fMRI). Methylphenidate. Psychostimulants.

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Financial disclosure:
K.R. has received speaker's honoraria from Lilly and Shire.

Acknowledgements:
K.R. has received support from the National Institute of Health Research (NIHR) Biomedical Research Centre (BRC) for Mental Health at South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, Kings College London. H.B. received post-doctoral support from an Action Medical Research grant to K.R. A.A.A. was supported by an Institute of Psychiatry PhD excellence award.

Accepted:
10.01.14.

How to cite this paper:
Rubia K, Alegría AA, Brinson H. Brain abnormalities in attention-deficit hyperactivity disorder: a review. Rev Neurol 2014; 58 (Supl 1): S3-18.

*Versión española disponible en www.neurologia.com*



## Introduction

Attention-deficit hyperactivity disorder (ADHD) is characterised by symptoms of age-inappropriate inattention, hyperactivity and impulsivity [1]. ADHD is one of the most common childhood psychiatric disorders, affecting 3-8% of school-aged children, with 65% of cases persisting into adulthood [2]. ADHD patients have deficits in higher-level cognitive functions necessary for goal-directed behaviors, so-called 'executive functions' (EF), that are known to be mediated by late developing fronto-striato-parietal and fronto-cerebellar networks [3]. The most consistent deficits are in motor response inhibition, sustained attention, and working memory [4,5] as well as timing processing, in particular time estimation [6,7] and temporal foresight, as measured in temporal discounting and gambling tasks [7].

## Objectives

ADHD is the most imaged child psychiatric disorder with over hundreds of published structural and functional imaging studies. This review discusses the most consistent deficit findings in brain structure, function and structural and functional connectivity. Furthermore, the review will cover current findings on disorder-specificity of these brain deficits in ADHD relative to other child psychiatric disorders. The effects of stimulant and non-stimulant medications on the brain structure and function of ADHD patients will also be reviewed and discussed. Last, we will discuss clinical applications of neuroimaging. This includes the use of multivariate pattern recognition analyses for imaging-based individual diagnostic classification of ADHD and neurotherapy methods that aim to upregulate dysfunctional brain regions in ADHD through neurofeedback or brain stimulation.

## Structural MRI studies

The vast majority of structural MRI (sMRI) studies have used region of interest (ROI) analyses, focussing on apriori hypothesised regions, typically with relatively liberally chosen thresholds. The most con-

sistent findings of a meta-analysis of ROI studies were reductions in total and right cerebral volumes, including several prefrontal regions, in the posterior inferior cerebellar vermis, the splenium, the corpus callosum, and the right caudate [8], which were also observed in later larger numbered sMRI studies [9-12]. A few recent ROI sMRI studies also found grey matter (GM) or cortical thickness abnormalities in subcortical limbic regions such as insula [13], amygdala [14] and thalamus [15]. These ROI-based meta-analytic findings confirm the notion that ADHD patients have deficits in fronto-striatal and fronto-cerebellar networks that mediate the late developing EF that are impaired in the disorder [16]. ROI studies, however, are biased towards apriori hypothesised regions. Whole brain imaging studies are more suitable to reveal the most consistent brain abnormalities without unnecessarily restricting the search volume. Three meta-analyses have been published on the remarkably few whole brain voxel-based morphometry (VBM) sMRI studies of ADHD. All studies showed that the right basal ganglia were consistently reduced in GM in ADHD relative to healthy controls [17-19]. In addition, the deficits were most pronounced in pediatric studies with adult studies not showing any deficits [18,19]. Given the extensive connections between the basal ganglia and frontal regions [16], a primary deficit in the basal ganglia, however, still implies fronto-striatal circuit abnormalities in ADHD [16]. These meta-analytic findings tie in well with our neurochemistry abnormality findings in ADHD based on a meta-analysis of positron emission tomography (PET) studies where we showed consistently reduced dopamine transporter levels in the basal ganglia in medication-naïve ADHD patients [20]. The only enhanced GM volume in ADHD patients relative to controls was in the precuneus, which is part of the default mode network (DMN) [18]. The DMN consists of intercorrelated co-activation of medial frontal lobe, anterior and posterior cingulate (ACC/PCC) and inferior temporal and parietal areas during rest, that are parametrically attenuated during cognitive load, and thought to represent 'mental clutter'. ADHD patients have more attentional lapses and attenuated deactivation of the DMN during attention tasks [21-23]. The enlarged volume size in this region could therefore be a plastic consequence of enhanced DMN activation (i.e. diminished deactivation).

In conclusion, the most consistent abnormality in ADHD patients based on whole-brain cross-sectional imaging studies is the reduced GM in the basal ganglia, with additional evidence for abnormal GM and cortical thickness abnormalities in frontal, temporal and cerebellar regions based on ROI studies.

It has been argued that ADHD children suffer from delayed brain maturation, due to their relative immaturity in behavioural features that diminish naturally with age such as impulsiveness and inattention and in cognitive functions that are mediated by late developing fronto-striatal and fronto-cerebellar systems [3]. Seminal longitudinal imaging studies from the National Institute of Mental Health (NIMH) provided direct evidence for this hypothesis by showing that 232 ADHD patients relative to 232 healthy controls had a delay in the peak of cortical thickness and surface area by 2-5 years, with the most prominent delay in frontal, superior temporal and parietal regions [11,24].

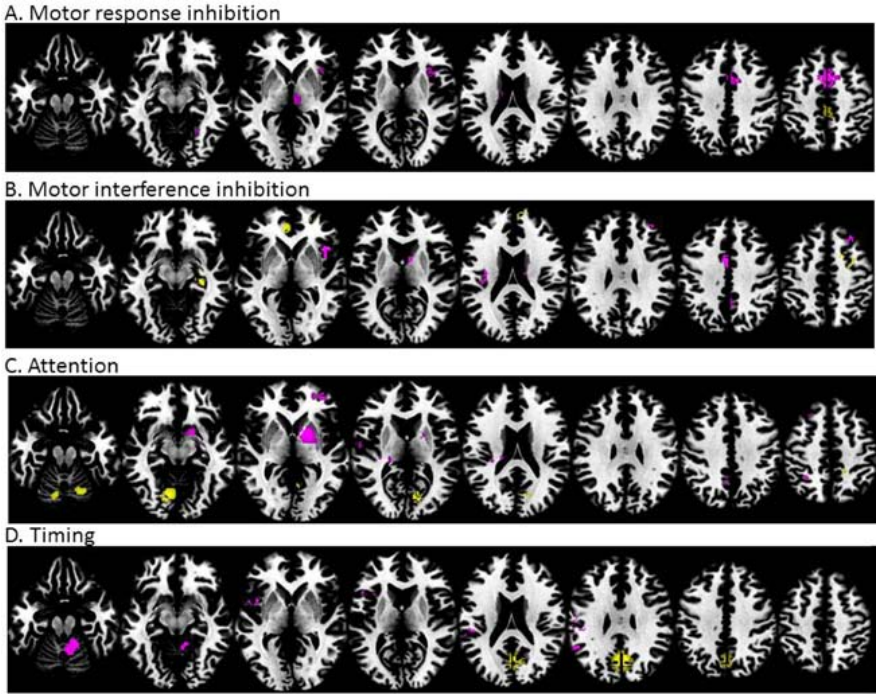
Diffusion tensor imaging (DTI) studies show that ADHD children and adults have deficits not only in isolated brain regions but in the white matter (WM) connectivity between these regions, most prominently between fronto-striatal, fronto-parieto-temporal, and fronto-cerebellar connections [25-30], as also shown in a recent meta-analysis of 9 DTI studies using whole brain analyses [31]. Furthermore these WM tract abnormalities, reflecting poor myelination or reduced axonal branching, have been related to clinical behavioural and cognitive abnormalities [30,32]. Consistent with the maturational delay hypothesis of ADHD, one study found slower development of WM in the caudate nucleus over adolescence in ADHD, which reached normal levels by adulthood [33] while 2 other studies that tested for a range of WM tracts, found almost all WM tracts to be attenuated in ADHD, and, given that most of these WM tracts develop well into mid-adulthood [34], hypothesised a possible global delay in WM tract development [35,36]. This will, however, have to be corroborated in longitudinal DTI studies.

## Functional MRI studies

Functional magnetic resonance imaging (fMRI) studies have provided consistent evidence for fronto-striatal, fronto-parietal and fronto-cerebellar deficits in ADHD during tasks of cognitive control with some emerging evidence for fronto-limbic abnormalities in the context of reward processing.

A meta-analysis of 55 whole-brain fMRI studies across EF, memory, reward and timing tasks in 16 adult and 39 pediatric studies, including a total of 741 ADHD and 801 control subjects, showed sig-

**Figure 1.** Four meta-analyses of fMRI studies of ADHD patients for different cognitive domains. The meta-analyses show underactivation in ADHD patients in several dissociated fronto-striatal and fronto-cerebellar networks during the respective cognitive domains. a) During motor response inhibition, ADHD patients show underactivation relative to healthy controls in the right ventral inhibition network, in right IFC, SMA, the basal ganglia and thalamus. They had enhanced activation in posterior cingulate gyrus [38]. b) During interference inhibition, ADHD patients had underactivation in right IFC, ACC, the basal ganglia and thalamus and enhanced activation in ventral anterior cingulate [38]. c) During attention tasks, ADHD patients showed reduced activation relative to healthy controls in the right dorsal attention network, comprising right DLPFC, the posterior part of the basal ganglia and thalamus, inferior parietal lobe and precuneus. ADHD patients have enhanced activation relative to controls in cerebellar and occipital regions [38]. d) During timing tasks, ADHD children had reduced activation in a predominantly left hemispheric timing network, comprising left IFC, left inferior parietal lobe and right cerebellum. ADHD patients had enhanced activation in a default mode region, the posterior cingulate cortex [22]. The enhanced activation in anterior and posterior cingulate could also reflect decreased activation of the default mode network in ADHD versus healthy controls.




nificant hypoactivation in ADHD relative to controls in bilateral ventral attention networks –inferior frontal cortex (IFC), basal ganglia– and predominantly right hemispheric fronto-temporo-parietal networks, including DLPFC/IFC, basal ganglia, thalamus, ACC and SMA. In addition, hyperactivation was observed predominantly in default mode regions as well as in visual and somatomotor regions [37]. Three other meta-analyses focused on specific cognitive domains. Thus, a meta-analysis of 21 whole-brain fMRI studies of cognitive and motor inhibition, including 7 adult and 14 pediatric studies, showed that 287 ADHD patients relative to 320 healthy controls had consistently reduced activation in key regions of inhibition, in right inferior prefrontal cortex (IFC), supplementary motor area (SMA), ACC, left striatum and right thalamus [38]. When separated by motor response and interference inhibition tasks, the SMA was more prominently underactivated for motor response inhibition and the ACC for interference inhibition (Figs. 1a, 1b). A meta-analysis on attention tasks included 13 mostly pediatric whole-brain fMRI studies and found underactivation in 171 ADHD patients relative to 178 healthy controls in the right hemispheric dorsal attention network, comprising the right DLPFC, right inferior parietal cortex and caudal parts of the basal ganglia and thalamus. In addition, ADHD patients had increased activation relative to controls in right cerebellum and left cuneus, pre-

sumably compensating for the underactivation of the frontal part of the dorsal DLPFC-parieto-cerebellar attention network [38] (Fig. 1c). A meta-analysis of timing functions in ADHD, including 11 fMRI studies showed consistently reduced activation in 150 ADHD patients relative to 145 healthy controls in left IFC, left inferior parietal lobe and the right lateral cerebellum [22], all key regions of timing functions [39]. The timing meta-analysis in addition also showed increased activation in ADHD patients in default mode regions, the PCC and precuneus [22] (Fig. 1d).

Interestingly, the brain regions that are underactivated in ADHD increase progressively in their activation with age [3], which could potentially reflect a developmental delay in brain function in ADHD patients. Problems deactivating the DMN have been associated with more attention lapses, both in normal development and in ADHD [23], and could also reflect a developmental delay [3]. Both the problematic deactivation of the DMN concomitant with poor activation of task-relevant and age-correlated brain activation may hence reflect a developmental delay of brain function and both are likely underlying the poor performance in ADHD patients in attention-demanding higher-level cognitive tasks.

In summary, the meta-analyses of whole-brain fMRI studies in ADHD show that ADHD patients have cognitive-domain dissociated deficits in multiple dorsal and ventral fronto-striato-parietal and fronto-cerebellar networks, including IFC-ACC/SMA-striato-thalamic networks for inhibitory control functions, right DLPFC-parieto-striato-cerebellar networks for attention functions and left IFC-parieto-cerebellar networks for timing functions [22,37,38] (Fig. 1). In addition, poor task-related activation appears to be concomitant with poor deactivation of the DMN, both of which are likely to underlie compromised performance in ADHD.

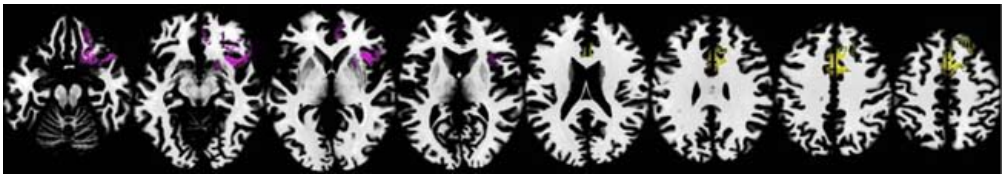
Abnormalities, however, have also been observed during reward processing. A meta-analysis of 8 ROI fMRI studies of reward anticipation in 340 ADHD patients and healthy controls, most of which used the same monetary reward anticipation task (MID), showed consistent underactivation of the ventral striatum in ADHD adults and children relative to healthy controls with a medium effect size [40]. An important caveat, however, is that deficits in ventral striatum have only been observed in ROI studies. Future large-scale fMRI studies will have to confirm the presence of abnormalities in the ventral striatum using whole brain image analyses.

In addition to deficits in the function of specific frontal, striatal, temporo-parietal and cerebellar regions, functional connectivity studies have demonstrated that ADHD patients also have abnormalities in the functional inter-regional connectivity between these regions both during rest and during cognitive tasks [41]. Thus, during the resting state, ADHD children have reduced functional connectivity in the DMN, mostly between ACC and PCC [42-45], as well as in fronto-striato-thalamic, fronto-temporal and sensorimotor circuitries [46-49]. An interesting double dissociation was observed between attenuated OFC-ventral striatum-limbic functional connectivity and emotion dysregulation and DLPFC-striato-cingulo-parietal functional connectivity abnormalities and poor EF [50]. Reduced functional connectivity has also been observed in children and adults with ADHD within fronto-striato-cerebellar networks during cognitive tasks such as sustained attention [51], inhibition, time estimation [52-54], working memory [55,56] and response preparation [57]. Furthermore, there is evidence for stronger coherence of the DLPFC with DMN and reduced anti-correlation between both in relation to poor attention performance, suggesting a more diffuse connectivity between functional networks in ADHD, where both DMN intrudes during attention-demanding contexts and DLPFC signalling is insufficiently suppressed in relation to DMN activity [21,58]. The findings from these functional connectivity studies suggest both abnormal task-based cortico-striatal-thalamic and abnormal DMN functional 'networks' that are poorly anti-correlated and together contribute to the cognitive and behavioural symptoms of ADHD. Given that DMN as well as task-based functional connectivity mature progressively with increasing age and are associated with progressive cognitive maturation [3,59], the more immature functional connectivity in these networks may reflect delayed functional brain maturation. This hypothesis was supported by a multivariate pattern recognition study that showed that the resting state functional connectivity abnormalities that classified ADHD adults relative to controls was similar to the pattern observed in younger typically developing subjects [60]. Future longitudinal fMRI studies will need to corroborate this hypothesis of a delay in the maturation of brain function and associated networks.

## Effects of stimulant and non-stimulant medications on the ADHD brain

Stimulant medication (e.g. methylphenidate or dexamphetamines) are first line treatment for ADHD

**Figure 2.** Most consistently increased brain activation within ADHD adolescents after a single clinical dose of psychostimulant medication relative to placebo or off-medication. The most consistent activation increase was in right inferior prefrontal cortex ($p < 0.005$) followed by increased activation in ventral ACC and the putamen ($p < 0.05$). There was a significant decrease of activation with placebo in dorsal ACC and supplementary motor area relative to stimulant medication, which could also potentially reflect increased deactivation of these regions for medication relative to placebo [65].



as they reduce the severity of ADHD core symptoms in up to 70% of patients [61]. Several fMRI studies have sought to further our understanding on the acute and chronic effects of stimulant medications on the function of the ADHD brain.

Several well-designed (e.g. randomised placebo-controlled, case-control crossover) whole-brain and ROI fMRI studies have examined the acute effects of Methylphenidate on brain function during a series of cognitive tasks in medication-naïve ADHD patients. An acute dose of methylphenidate in medication-naïve or in chronically medicated ADHD youth has been shown to increase and normalise the underactivation in right and/or left IFC as well as ACC during motor and interference inhibition [62-66], timing [6,65,67], error processing [64] and sustained attention [51], but had no effect during working memory [68,69]. Effects were also observed in the cerebellum during time discrimination [6], interference and motor inhibition [64-66] and attention tasks [51]; and in the striatum during reward [51] and response inhibition tasks [64-66,70].

Our meta-analysis of all 14 published whole-brain fMRI studies that tested the effects of stimulants on brain function in ADHD showed that the most consistent acute effect is the increased activation of right IFC/insula, with additional effects in the putamen at a more lenient threshold [65] (Fig. 2). A few studies investigated the acute effects of stimulants on functional connectivity and found that an acute dose of methylphenidate normalized functional connectivity deficits in fronto-striatal, fronto-parietal and fronto-cerebellar networks during vigilant attention [51], in fronto-parietal networks during working memory [55], in ventral ACC and lateral PFC connectivity during a cognitive Stroop task [54] and between the amygdala and lateral PFC [71] during an emotional Stroop task.

Relatively little, however, is known about chronic effects of psychostimulants. A 12 months trial of stimulant administration in children with ADHD normalized the enhanced (potentially compensatory) activation in insula and putamen during a reorienting attention process. Also, there was a trend for ACC dysfunction to be more pronounced in 5 unmedicated relative to 9 chronically medicated patients, suggesting long-term amelioration [72]. OROS methylphenidate over 3 months normalized reduced ventral striatum and thalamus activation during the processing of low but not high reward outcomes [73]. In adult ADHD, a 6-week trial of stimulant medication compared to placebo increased activation in the dorsal ACC, DLPFC, premotor and parietal cortices, caudate, thalamus and cerebellum during interference inhibition [74]. Our meta-regression analyses across fMRI studies of attention and inhibition found that long-term stimulant administration (between 6 months to 3 years) was associated with normalization of right caudate activity during attention [38] and of right DLPFC activity during timing tasks [22].

In conclusion, the meta-analytic findings suggest that acute and longer-term stimulant medication treatment is most consistently associated with an upregulation of two key dysfunctional areas in ADHD, the right IFC and the basal ganglia.

Unfortunately there are no prospective longitudinal imaging studies of long-term stimulant effects on brain structure. However, retrospective comparisons of medicated and non-medicated ADHD patients suggest that medicated patients with ADHD have more normal size, volumes and/or morphology than unmedicated patients in ADHD-relevant

brain regions including the right ACC [75]; the anterior thalamic pulvinar [15]; the posterior inferior vermis of the cerebellum [76]; the left lateral cerebellar surface [77]; the basal ganglia [78]; and the corpus callosum [79]. Two studies of retrospective comparisons within longitudinal data found more normal WM [80], and a less rapid cortical thinning development in left IFG, premotor and parietal regions in long-term medicated relative to non-medicated children [81]. However, there have also been negative findings in relatively small sampled studies [9,82]. Two meta-regression analyses of VBM studies tested for long-term medication effects. Both studies found that long-term stimulant medication was associated with more normal basal ganglia volumes in ADHD [18,19].

In conclusion, overall sMRI and fMRI studies suggest that stimulant medication may potentially be neuro-protective on brain structure and function. Studies that have tested for neurochemical effects, however, have been less promising. Our meta-analysis of PET studies in mostly adult ADHD patients, showed that long-term stimulant medication was associated with an abnormally increased level of striatal dopamine transporters, which were reduced relative to healthy controls in medication-naïve patients, suggesting potential brain adaptation to stimulants [20]. This was also observed in 10 adults with ADHD in a within-subject study design after a one year follow-up of chronic stimulant medication treatment [83]. These findings of plastic long-term upregulation of DAT with chronic stimulant medication could explain relatively poor long-term efficacy of stimulant medication [84]. However, prospective longitudinal imaging studies within a randomized placebo-controlled design are crucial to confirm these findings of plastic effects based on cross-sectional comparisons on brain structure, function and neurochemistry.

Very few studies have tested brain effects of the only other licensed medication for ADHD, atomoxetine. In a placebo-controlled randomized study, we found shared effects of atomoxetine and methylphenidate of upregulation of right IFC activation during time discrimination and of bilateral IFC activation during inhibition, which was furthermore normalised with both drugs in their underactivation in ADHD patients under placebo relative to healthy controls [62,67]. Both drugs also elicited compensatory fronto-striato-thalamic overactivation in ADHD children during working memory and both drugs deactivated DMN activation [68]. Drug-specific effects, however, were also observed with atomoxetine upregulating and normalised right DLPFC underactivation during working memory [68] and Methylphenidate increasing compensatory activation in left IFC and the basal ganglia during response execution and one of the WM conditions [68]. Furthermore, methylphenidate had drug-specific effects on the activation of the dopaminergically innervated SMA during motor response execution and time discrimination [62, 67]. A few recent fMRI studies tested chronic effects of atomoxetine. The only pilot study in adult ADHD showed that atomoxetine treatment of 6 weeks increased activation in ROIs of DLPFC, parietal cortex and cerebellum but not in dorsal ACC [85]. A comparative fMRI study using a parallel group design in 36 ADHD patients found that a shared association between clinical improvement after 6-8 weeks of both drugs and reductions in bilateral primary motor cortex activation. There was, however, also a drug-dissociated association in right IFG, left ACC/SMA and bilateral PCC cortex which were all enhanced in activation in relation to clinical response to atomoxetine but decreased in activation in relation to clinical response to methylphenidate [86]. Last, a preliminary analysis found that chronic methylphenidate response in 7 ADHD adolescents was associated with acute stimulant reduction effects in parietal regional homogeneity during rest [87]. Future larger powered imaging studies using multivariate pattern recognition methodology are needed, however, to provide better estimates of whether baseline imaging deficits can predict medication response.

In conclusion, both psychostimulants and atomoxetine appear to enhance the activation of right IFC, presumably via their shared mechanism of action on catecholamines in frontal brain regions, but they seem to also have drug-specific effects in other frontal and subcortical regions. Further studies, however, are needed to disentangle the shared and specific drug effects of atomoxetine relative to stimulant medication on ADHD brain function.

## Disorder-specificity of ADHD brain abnormalities compared to other childhood disorders

For neuroimaging to be clinically relevant it is crucial to establish 'disorder-specific' biomarkers that can help with differential diagnosis and differential treatment decisions. The childhood pathology that is most commonly comorbid with ADHD is CD/ODD. However, hardly any imaging studies have controlled for CD/ODD and hence the ADHD im-

aging literature is confounded by this comorbidity. Two sMRI studies compared the two disorders. One found no disorder-specific differences between comorbid children with ADHD with and without CD, but shared volume reductions in posterior and inferior cerebellar vermis [88]. The other study found reduced GM in several frontal and parietotemporal regions in CD relative to ADHD and control children, while ADHD patients had only reduced regional GM deficit in a left dorsolateral/precentral prefrontal lobe region relative to controls. Also there was a shared GM deficit between both disorders in left dorsolateral/precentral gyri. However, all analyses were conducted at uncorrected thresholds and the ADHD findings were not consistent with the prior literature [89]. A series of fMRI studies from our lab compared well differentiated medication-naïve and IQ-matched groups of children with non-comorbid CD and non-comorbid ADHD during 5 disorder-relevant executive function tasks of response and interference inhibition, sustained attention, saliency detection and cognitive switching. Despite no performance differences, in 4 of the 5 tasks, patients with ADHD had disorder-specific reduced activation compared to both healthy controls and CD patients in the IFC/DLPFC [90-93]. CD children, on the other hand, showed underactivation in paralimbic regions during all tasks, including temporal lobe during performance monitoring [93], the ventromedial prefrontal cortex during reward [90] and limbic areas during sustained attention [90], in line with consistent evidence for structural and function deficits in CD in the paralimbic system, comprising ventromedial OFC and interconnected limbic structures that mediate motivation and affect control [4]. Two studies compared ADHD children with and without CD and psychopathy traits, and found that the comorbid group only had reduced amygdala activation and reduced connectivity between amygdala and vmPFC in relation to fear [94], but enhanced activation in vmPFC during punished reversal errors [95]. Therefore it appears that there are disorder-specific and process-related dissociations in prefrontal lobe deficits, with ADHD children having consistent problems with the recruitment of lateral IFC/DLPFC systems in the context of 'cool' executive inhibitory and attention control, whereas CD children have problems with the recruitment of 'hot' ventromedial OFC-limbic systems that mediate motivation [4].

Disorder-specific reduction in IFC activation in children with ADHD was also observed when compared to children with obsessive-compulsive disorder (OCD) during tasks of motor response inhibition and switching [96,97]. OCD patients, in turn, had shared abnormalities with ADHD patients in the OFC and DLPFC [96,97]. During a saliency task inverse activation patterns were observed with PCC and basal ganglia being underactivated in ADHD relative to OCD, who had increased activation in these regions relative to controls and ADHD boys [97], in line with evidence for diminished saliency processing in ADHD, but enhanced saliency processing in OCD. While no structural studies have directly compared between OCD and ADHD, two meta-analyses of VBM studies in each disorder showed differential abnormalities in the basal ganglia, which were reduced in GM in ADHD [18], but enhanced in OCD [98].

Two sMRI and 2 fMRI studies have compared adolescents with ADHD and autism spectrum disorder (ASD). The first sMRI study found shared abnormalities in limbic and parietal regions which, however, did not survive correction for multiple testing [99]. A study using multivariate pattern recognition analysis found relatively high specificity of about 80% of classifying ADHD patients relative to both controls and ASD patients based on brain patterns of later developing lateral fronto-striato-cerebellar networks for the classification of healthy controls and of earlier developing ventromedial fronto-limbic regions for the classification of ADHD patients [100]. A task-based fMRI study showed shared dysfunction in DLPFC-striato-thalamic regions and shared problems with the deactivation of the DMN in both disorders during a parametric sustained attention task. ASD patients, however, had presumably compensatory increased cerebellar activation and less pronounced DLPFC underfunction relative to ADHD, which may underlie their spared task performance deficits which were only observed in ADHD [21]. A resting state fMRI study reported shared network centrality abnormalities in precuneus for both disorders, but ADHD-specific increases in degree centrality in right striatum/pallidum relative to controls and ASD, while ASD-specific increases in degree centrality were observed in predominantly left temporo-limbic areas, which are typical areas for socio-emotion processing that have consistently been found to be abnormal in ASD [101].

Several imaging studies have compared ADHD with bipolar disorder (BD). Two pediatric sMRI studies found contrasting associations of decreased volumes of caudate and putamen with ADHD and increased volumes of caudate, putamen, globus pallidus and ventral striatum as well as additional lim-

bic abnormalities with BD [102,103]. The comorbid group was either non-impaired [102] or more like the pure BD group [103]. Two adult sMRI found that pure ADHD was associated with reduced GM volumes and cortical thickness in prefrontal, cingulate, parieto-temporal and cerebellar regions, whilst pure BD was associated with smaller left orbital prefrontal and larger right thalamic and parieto-temporal regions [104,105]. In both studies the comorbid disorder showing combinatorial deficits [104,105]. A third study showed that BD alone was associated with thinning in middle, ventral PFC and ACC, while an interaction effect between both disorders was observed in the thinning of left OFC and subgenual ACC [106]. Last, a DTI study testing for differences in 8 fiber tracts reported reduction in 7 WM tracts in ADHD, while BD had shared abnormalities with ADHD in only one of the frontal WM tracts, i.e., the anterior corona radiata and the splenium, connecting posterior attention regions [35]. The findings suggest a global dysmaturation of WM tracts in ADHD, with more specific abnormalities in frontal and parietal WM tracts in BD. Overall, the structural imaging studies show more prominent OFC-limbic abnormalities for BD and more prominent lateral fronto-striato-parieto-temporal deficits in ADHD and differential basal ganglia volumes sizes (enlarged in BD and reduced in ADHD). Similar findings have been observed in fMRI studies. During inhibition tasks, ADHD children showed decreased activation relative to BD in typical inhibition regions of IFG/VLPFC, DLPFC and temporo-parietal regions, whereas BD children had reduced occipital and postcentral activation relative to ADHD [107]. During an emotional valence Stroop task, ADHD patients had reduced VLPFC activation relative to healthy controls while BD relative to healthy controls and ADHD showed increased activation of the VLPFC and ACC [107]. During an affective 2-back working memory task, BD patients had increased activation in bilateral caudate relative to ADHD for happy faces, while for angry faces, the BD group showed increased activation relative to the ADHD group in emotion-regulation areas of left medial OFC and left subgenual ACC, whereas the ADHD group showed increased activation in 'cool' EF working memory regions of DLPFC and SMA [108]. Overall, both the structural and functional comparisons suggest that the emotional impulsiveness of non-comorbid BD is more consistently associated with OFC-limbic abnormalities, while the cognitive impulsivity of ADHD appears to be associated with 'cool' abnormalities in cognitive VLPFC/IFC-striato-parietal circuits [109].

In conclusion, relatively few and small-sampled studies have compared between ADHD and other disorders. There is evidence that ADHD patients have more pronounced dysfunctions in lateral IFC/DLPFC relative to CD, OCD [4], BD [109] and possibly ASD [21]. In addition, there is evidence that the basal ganglia structure and function may be different between ADHD and both BD and OCD [18, 97,98,102,103,108]. Future larger sampled comparisons in groups of non-comorbid and comorbid patients, however, will be necessary to establish disorder-specific structural and functional biomarkers.

## Clinical application of neuroimaging in ADHD

Despite consistent evidence for brain structure and function deficits in ADHD, currently ADHD is diagnosed solely on the basis of subjective clinical and rating measures, which are often unreliable. Attempts to find objective neuroimaging biomarkers for ADHD, however, have been limited by the use of traditional univariate group statistical analyses, where subjects in both groups typically overlap and effect sizes are small. In contrast, multivariate pattern analyses for imaging data can make predictions (e.g. of class membership) for individual subjects as opposed to group-level inferences and have been successfully applied to other disorders [110].

To date, few imaging studies have used multivariate pattern recognition analyses techniques to classify ADHD patients. A recent competition to apply multivariate methods on a multicenter resting state functional and anatomical imaging dataset of 285 children and adolescents with ADHD and 491 healthy controls (ADHD-200 Consortium; http://fcon_1000.projects.nitrc.org/indi/adhd200/) was met by a range of classification approaches [111-114]. Accuracies derived by internal cross-validation ranged from 55-78% [114].

A few recent studies used probabilistic classification models such as Gaussian Process Classifiers (GPCs), which provide estimates of predictive uncertainty and can accommodate unbalanced diagnostic settings or variations in disease prevalence, which are crucial for clinical applications [115,116]. Three studies from our lab used GPC in structural and functional imaging data in adolescents with ADHD and showed a relatively high overall classification accuracy of between 75% and 80% with relatively small numbers of between 20 and 33 patients [100,117,118]. Interestingly, across all studies the brain structure and function patterns that classified controls were in later developing lateral

fronto-striato-parieto-cerebellar networks, while patterns that classified ADHD were in earlier developing ventromedial prefrontal and limbic regions [100,117,118]. Importantly, one of the studies showed that the classification accuracy was disorder-specific compared to ASD adolescents [100], which is crucial for the potential future use of neuroimaging as an aid for 'differential' diagnosis. Another recent study used a semi-supervised clustering algorithm based on the spatial patterns of variation across the morphological surfaces of numerous cortical and subcortical brain regions to disorder-specifically diagnose, with relatively high accuracy of almost 90%, youth with ADHD relative to Tourette syndrome [119]. These studies are a promising first step towards the translational use of neuroimaging as a potential differential diagnostic aid. Future studies will have to test whether classification algorithms are stable across patient population, countries and scanners as well as their ability to classify ADHD subgroups and to determine disorder-specific classification. While imaging-based classification algorithms are unlikely to replace clinical assessment and diagnosis, they may be a useful objective, automated, and reliable complementary diagnostic tool that could reduce variability in clinical practice and, ultimately, help to improve diagnostic accuracy. They also have the potential to help with prognosis of disease progression or treatment choice.

## Discussion

The last two decades of neuroimaging have significantly broadened our understanding of the underlying neurobiology of ADHD. They have shown that ADHD is most prominently associated with the dysmorphology, dysfunction and underconnectivity of multiple fronto-striato-parietal and fronto-cerebellar networks that mediate 'cool' EF, such as the ventral fronto-ACC/SMA-striato-thalamic cognitive control system, the dorsal and ventral fronto-striato-thalamo-parieto-cerebellar attention systems and ventral fronto-striato-parieto-cerebellar timing networks. In addition, ADHD children have structural, functional and connectivity deficits in DMN systems that appear to be poorly deactivated during task performance and hence to intrude upon task-positive cognitive systems, leading to impaired EF. Furthermore, there is emerging evidence for OFC-limbic abnormalities in the context of reward processing, with particular implication for the ventral striatum, which, however, needs to be confirmed in larger-scale imaging studies, given that the findings are based on ROI analyses and confounded by comorbidity with CD. There is evidence for a delay in normal brain maturation from structural imaging studies, with indications that this may also apply to brain function and structural and functional connectivity. Studies on the clinically relevant question of disorder-specificity of imaging biomarkers for ADHD are only just emerging, but point towards potential disorder-specificity of ventral prefrontal under-recruitment relative to CD, OCD and BD [4,109] as well as of differential basal ganglia deficits relative to OCD and BD [18,109].

fMRI studies have shown that the most consistent mechanism of action of psychostimulants in ADHD is the upregulation and normalisation of the activation of the IFC and the basal ganglia. Studies on atomoxetine effects on brain function have only just emerged, but acute effects on prefrontal systems appear to be similar to those of psychostimulant medication. Some evidence from retrospective comparisons suggests long-term plastic medication effects on brain structure, function and neurochemistry, which, however, need to be confirmed in prospective randomized controlled designs. PET studies will need to investigate the underlying neurotransmitter abnormalities in ADHD other than the DA system, such as the serotonin, noradrenalin, glutamate and GABA systems with a particular emphasis on how they interact with the dysfunctional DA system.

The imaging literature of ADHD is confounded by relatively small numbers of often non-representative samples of convenience, by the use of ROI analyses and liberal uncorrected thresholds and by uncontrolled comorbidity with CD/ODD. Adult studies suffer from comorbidy confounds with secondary affective conditions and ascertainment bias from clinics, which do not capture remitted cases. The majority of imaging studies have been conducted in long-term medicated patients, which, as discussed, has an effect on structure and function, and is hence a crucial confound.

Given that cross-sectional imaging studies are confounded by cohort effects and ascertainment bias, there is an urgent need for longitudinal imaging studies, in particular following up children with ADHD into adulthood, to understand brain mechanisms of remittance and persistence. Furthermore, future studies will need to focus on multimodal imaging in representative populations to enhance our holistic understanding on the relationship between structural, functional, connectivity, blood flow as well as brain chemistry abnormalities within the

same patient groups. Also, future studies will need to focus on understanding the (differential) neurobiological basis of different ADHD subtypes as well as comorbid cases. Future studies therefore ideally should be longitudinal, multimodal, and tied to epidemiological samples.

Clinical translation of neuroimaging will be the challenge over the next decade. Several pioneering machine learning approaches using GPC have been promising, showing relatively high accuracy of up to 80% in classifying ADHD patients relative to controls and ASD patients based on structural or functional imaging scans. Multimodal multivariate approaches including several imaging as well as non-imaging modalities may provide higher classification accuracies than unimodal studies [110]. These multivariate classification methods, if successful and replicated across different representative patient groups, scanners and demographic populations, may be able to help with future imaging-based diagnosis or prognosis of individual patients and provide brain-based patient stratification and more personalised medicine.

Last, there is high potential for using neuroimaging as a neurotherapy. EEG-based neurofeedback has been shown to have similar effect sizes to stimulant medication in reducing ADHD behaviours [120]. fMRI or near infrared-spectroscopy (NIRS) have better spatial resolution and combined with neurofeedback could be used to upregulate the activation of ADHD-specific dysfunctional brain regions such as IFC, DLPFC and the basal ganglia (with fMRI only). Likewise, regional electrical stimulation via repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) have been successful in other psychiatric disorders [121] and are promising for ADHD. So far, only one pilot study tested rTMS over right dorsolateral prefrontal cortex in one single session in 13 ADHD adults and found increases in behavioural attention scores [122].

In conclusion, we have acquired substantial knowledge on the underlying neurobiological mechanisms of ADHD. However, more studies are needed that integrate different imaging modalities to understand the interplay between the changes in neurochemistry, brain function and brain structure and to assess longitudinal trajectories of the disorder. The next decade will need to focus on using neuroimaging techniques in a more clinically applied fashion, either to aid with individual diagnosis, prognosis of disease progression and treatment success or as a neurotherapy to normalise abnormally functioning brain regions.

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## Anomalías cerebrales en el trastorno por déficit de atención/hiperactividad: una revisión

**Objetivo.** Revisar los hallazgos de los estudios con resonancia magnética en el trastorno por déficit de atención/hiperactividad (TDAH) infantil y adulto.

**Desarrollo.** Dichos estudios han demostrado que el TDAH se caracteriza por la presencia de múltiples anomalías de carácter estructural y funcional, primordialmente en los circuitos frontoestriatales, pero también en los circuitos frontoparietotemporales, frontocerebelares e, incluso, frontolímbicos. Los datos aportados por los estudios longitudinales de resonancia magnética estructural demuestran que el TDAH se caracteriza por un retraso en la maduración estructural del cerebro. Esta conclusión se ve reforzada por los indicios indirectos ofrecidos por los estudios de cortes transversales, que indican la existencia de una inmadurez sustancial tanto en la función cerebral como en los patrones de conectividad estructural y funcional, indicios que, sin embargo, están pendientes de confirmar en estudios longitudinales. La alteración funcional de la corteza prefrontal ventrolateral parece estar más afectada en el TDAH que en otros trastornos pediátricos, y existen algunos indicios de anomalías distintivas en los ganglios basales. Un metaanálisis sobre los efectos de los estimulantes en la función cerebral demuestra que el mecanismo de acción agudo más congruente de los fármacos psicoestimulantes consiste en el aumento de la activación de la corteza prefrontal inferior y los ganglios basales. Los primeros intentos por utilizar los datos de los estudios de neuroimagen para elaborar clasificaciones diagnósticas individuales de los niños con TDAH a partir de técnicas de reconocimiento de patrones han cosechado resultados alentadores, pero todavía deben ser replicados por más centros y aparatos de resonancia magnética.

**Conclusiones.** Durante los últimos 20 años, las técnicas de neuroimagen han perfilado los biomarcadores del TDAH, pero es necesario que nuevos estudios descubran la utilidad clínica de esa información, como el uso de tales técnicas como instrumento de clasificación diagnóstica y pronóstica individualizada o como terapia para revertir las anomalías de la función cerebral que han sido confirmadas durante los dos decenios anteriores.

**Palabras clave.** Atomoxetina. Imágenes con tensor de difusión (DTI). Metilfenidato. Psicoestimulantes. Resonancia magnética funcional (RMf). Trastorno por déficit de atención/hiperactividad (TDAH).