

ADHD: What have we learned from Neuroimaging?

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Abstract

The last two decades of modern imaging techniques applied to research into attention deficit hyperactivity disorder (ADHD) have substantially expanded our knowledge of the underlying neural substrates of this condition and have shed light on the mechanism of action of the most common treatment of the disorder, stimulant medication. Studies have shown that ADHD is a multisystem disorder affecting several late developing fronto-cortical and fronto-subcortical pathways that mediate mature adult behaviour and cognition. Psychostimulants appear to modulate brain catecholamines and to have a normalising impact on some of the brain deficits in ADHD. The challenge lies in finding avenues to use neuroimaging techniques in clinical practice to aid diagnosis, treatment and prediction of response to treatment of ADHD.

Key words: ADHD, fMRI, MRI, methylphenidate, psychostimulant medication, frontal lobes, basal ganglia, cerebellum, parieto-temporal regions.

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is characterised by age-inappropriate symptoms of inattention, impulsiveness and hyperactivity (DSM IV) (1). It disrupts academic and social development, and is associated with significant psychiatric comorbidities and mental health problems in adult life (2). ADHD affects 5% of school-aged children worldwide (3) and persists into adulthood in 65% of cases affecting 4% of the adult population (4).

Impairment of Executive Functions

Both children and adults with ADHD have been found to be impaired in executive functions (EF) which develop late in life and are necessary for mature adult goal-directed behaviour, such as inhibitory control, cognitive flexibility, attention, working memory, planning, decision making and temporal foresight (5). These functions are mediated by neural networks comprising the frontal lobes, the basal ganglia and parieto-temporal regions that develop late in their structure and function (6, 7).

Neuroimaging and brain abnormalities

ADHD was originally considered a mild disorder, labelled “minimal brain disorder” in the seventies. Given that impulsivity, inattention and hyperactivity naturally diminish with age, it was observed that children with ADHD behave like younger children and it was hypothesised that ADHD might therefore be a delay of normal brain development. It was also hypothesised that ADHD patients suffer from deficits in prefrontal brain regions, based on the observation that patients or animals with frontal brain lesions can develop impulsiveness and/or ADHD-like symptoms. Furthermore, the chance discovery that methylphenidate (MPH) and other psychostimulants are effective in reducing the clinical symptoms of the disorder led to the suggestion that the basal ganglia must be affected too, given that MPH manipulates dopamine levels in the basal ganglia.

The last two decades of application of modern neuroimaging techniques such as positron emission tomography (PET) and magnetic resonance imaging (MRI) to ADHD research has substantially revolutionised our knowledge of the underlying neural substrates of ADHD. Neuroimaging of ADHD has proved direct evidence for these early theories of fronto-striatal deficits but, most importantly, has substantially widened our knowledge on the underlying brain abnormalities, revealing that ADHD is

more than a problem of frontal and striatal deficits.

Structural imaging studies have shown that children and adults with ADHD, relative to healthy controls, have abnormalities not only in several late-developing fronto-striatal networks but also in temporo-parietal and fronto-cerebellar neural networks which mediate the above-mentioned cognitive control functions that are impaired in this disorder. Thus, reduced volume and cortical thickness have been observed in several frontal brain regions, parieto-temporal areas, the basal ganglia, the cerebellum and the splenium of the corpus callosum (for review see (8); for meta-analysis of region of interest studies see (9)). Two subsequent meta-analyses of whole-brain morphometry studies in children and adults with ADHD found that the most consistent regional grey matter reduction in ADHD patients compared to controls were in the basal ganglia (10, 11). Most interestingly, both age and psychostimulant medication were associated with the structural deficits, so that older adult patients were no longer impaired in their basal ganglia volumes, and equally, studies that included a high proportion of patients who had been chronically medicated, also no longer showed any structural abnormalities (11). These findings suggest that basal ganglia deficits normalise both with age and with chronic psychostimulant medication. Longitudinal imaging studies have furthermore provided evidence that the structural abnormalities observed in children with ADHD compared to healthy peers in frontal, striatal, parietal and cerebellar regions may be due to a delay in structural brain maturation (12, 13). This finding was seminal, given that it provided the very first scientific evidence for the 40 year old observation-based hypothesis of a delay in brain maturation.

Diffusion tensor imaging studies measure the integrity of white matter tracts, thus providing a measure of structural interconnectivity. These studies have shown global deficits in patients with ADHD in late-developing white matter tracts connecting fronto-striatal, fronto-parietal, fronto-cerebellar and parieto-occipital regions, assumed to reflect late brain maturation. These studies provide evidence for widespread abnormalities at the neural network level, and not only in isolated brain regions (14).

Underactivation of regions of the brain

Functional MRI (fMRI) studies investigate the brain while in action, e.g. while patients perform cognitive tasks in which they are known to be compromised. fMRI studies have provided evidence that these fronto-striatal, as well as parieto-temporal and cerebellar regions are not only structurally abnormal but also under-functioning in ADHD patients relative to controls. Children and adults with ADHD have shown underactivation relative to controls in several prefrontal regions, most prominently the dorsolateral and the inferior frontal cortex, but also in the anterior cingulate, the basal ganglia, the supplementary motor area, the cerebellum and temporo-parietal cortices during compromised functions, such as inhibition, attention and timing functions (for reviews see (8, 15, 16)). More recent studies have also provided evidence for functional deficits in ADHD patients in the orbitofrontal and limbic brain regions during tasks of motivation, suggesting deficits in fronto-limbic areas that mediate the control of motivation and affect (8, 15, 16). Recently developed functional connectivity fMRI analyses allow the investigation of the extent to which brain regions work together functionally. These studies have shown that brain regions are less functionally interconnected in ADHD, both during the resting state and when they perform cognitive tasks (14). Together with the DTI studies that show underdeveloped white matter tracts, these studies suggest that both the “software” and the “hardware” are wired less effectively in ADHD patients relative to controls (14).

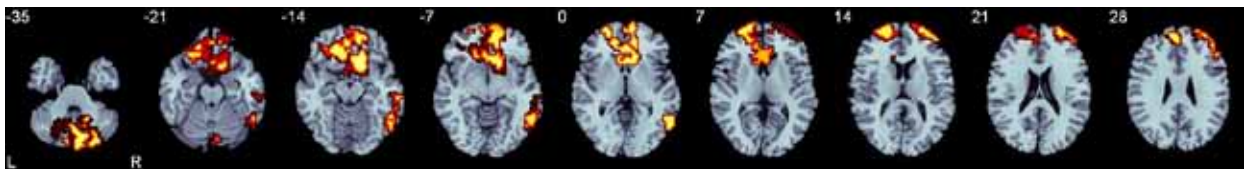
In conclusion, MRI neuroimaging has substantially widened our horizon with respect to the underlying neurobiological deficits in ADHD. We have moved from the notion of a disorder of fronto-striatal deficits to the notion of a disorder with relatively widespread neural deficits in multiple interconnected systems of the brain that are important for adult mature behaviour including inhibitory (fronto-striatal deficits), attention (parieto-temporal regions), and motivation control (fronto-limbic networks) as well as timing functions (fronto-striato-cerebellar networks).

How do the psychostimulants work?

Another important contribution of modern neuroimaging has been the understanding of the brain mechanisms of the action of psychostimulants. Psychostimulant therapy is the most effective pharmacological treatment for ADHD, improving clinical symptoms in 70% of patients (17). PET studies have shown that methylphenidate, the most commonly used psychostimulant, blocks up to 70% of striatal dopamine transporters in both those with ADHD and healthy adults, enhancing striatal dopamine availability, with additional catecholamine-enhancing effects in the frontal regions (17). PET studies have provided further evidence that ADHD patients suffer from abnormal striatal dopamine transporter levels, that are important for cognitive and motivation functions, although findings have been inconsistent with respect to whether these are elevated or reduced (17).

A recent meta-analysis of PET studies showed that dopamine transporter levels in ADHD patients are elevated, but this is associated with psychostimulant effects, so that patients who have been long-term medicated have elevated dopamine transporter levels, while medication-naïve patients have reduced levels (18). This suggests that the brain undergoes plastic changes in neurotransmitter transporter density in response to long-term medication. This is parallel to the above-mentioned findings of more normal structure in the basal ganglia in long-term medicated ADHD patients, suggesting that long-term medication has a neuroplastic effect on both brain structure and brain chemistry. While the functional significance of the elevation of dopamine transporter levels after long-term medication is unclear, the more normal brain structure after long-term medication needs to be seen as a positive development. It suggests that fears by parents, patients and practitioners of a negative impact of medication on normal brain development may be unjustified, with medication appearing to have positive rather than negative effects on the structural brain development of ADHD. This is also hinted at by other individual studies that show that long-term medicated ADHD patients have more normal brain structure than medication-naïve patients in other brain regions, such as the frontal and parietal lobes (19), cerebellum (20) and anterior cingulate (21). See Figure 1.

a) Underactivation in ADHD boys under placebo relative to healthy boys



b) no differences in brain activation in ADHD boys relative to healthy boys after one single dose of Methylphenidate

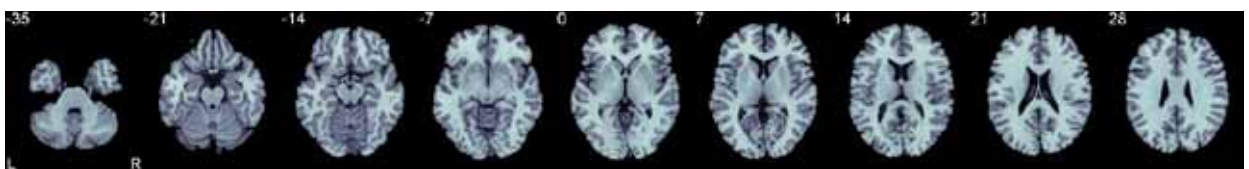


Fig 1. a) Underactivation in ADHD boys under placebo relative to control boys in Medial frontal cortex, basal ganglia, cerebellum and temporal regions during time estimation
b) Under Methylphenidate brain activation differences are no longer observed between ADHD and healthy boys. Data are from Rubia et al., *Phil Trans B*, 2009, 364, 1919-1931.

Functional imaging studies also show that both the short-term as well as the long-term administration with MPH upregulates and even normalises fronto-striatal, cerebellar and parietal brain function in ADHD patients (22-26). Longitudinal randomised controlled studies, however, are needed to corroborate these findings from cross-sectional studies that are confounded by selection bias.

What have we learned so far?

In conclusion, neuroimaging has substantially expanded our knowledge on the underlying substrates of ADHD, showing that the disorder is characterised by relatively widespread and presumably immature changes in fronto-striatal but also other fronto-subcortical and fronto-cortical neural networks that mediate the behavioural and cognitive abnormalities that characterise the disorder. Neuroimaging has also provided us with some insights into the underlying abnormalities of the dopamine system of the disorder and the mechanism of action of the most commonly used dopamine-agonist treatment of ADHD. Important tasks, however, still lie ahead. For neuroimaging to be clinically useful, it needs to help with diagnosis, prognosis and treatment.

Looking into the future

Future neuroimaging studies need to investigate the disorder-specificity of these structural and functional deficits in order to establish objective disorder-specific biomarkers that can classify individual patients and potentially aid in clinical diagnosis. PET studies will be needed to investigate abnormalities in other neurotransmitters such as the serotonin, noradrenaline, glutamate and GABA in order to develop novel and more targeted pharmacological treatment. Gene-imaging interaction studies could potentially establish the genetic risk for brain abnormalities, for disorder trajectory or for treatment response. Finally, functional neuroimaging techniques in combination with neuro-feedback or brain stimulation techniques such as transcranial magnetic stimulation (TMS) could potentially be used directly as non-pharmacological treatment for ADHD to upregulate those brain regions that neuroimaging has found to be under-functioning in ADHD.

GP Comment.

What have I learned from this paper?

1. The whole concept of mental disorder may be considered controversial as there are often no physical signs to establish a diagnosis. However, this article describes our advancing knowledge in brain structure and functioning to aid diagnosis, prognosis and treatment.
2. It is interesting and also of great concern that neuro-imaging has revealed much more extensive structural and functional brain abnormalities in ADHD than originally suspected.
3. I am reassured that neuro-imaging appears to show that long-term stimulant medication may improve brain function and structure. GPs are expected to continue prescribing medication when stabilised by a specialist and this offers hope that we are acting in the best interests of the patient and their families. However, I agree with the author that there is still much to learn! I wonder if 'normal' brain structure equates to 'normal' behaviour and how is 'normal' defined?
4. Does drug treatment result in improved long-term health outcome?
The real challenge for researchers is to establish a causal relationship between long-term health outcome and the process of care - i.e. psychological, social, educational or pharmaceutical. Assuming a bio-social-psychological model of health, how do researchers ensure results are not confounded by a myriad of unknown external variables outside their control?
5. As ultimate health outcome is influenced by patient experience and their subjective perception of care received, it might be suggested that qualitative research methods as well as quantitative tools are required.

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