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Functional magnetic resonance imaging in attention deficit hyperactivity disorder (ADHD): a systematic literature review

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Abstract

fMRI research in ADHD is a fast developing and very complex field. Every study appears to show differences in patterns of brain activation between cases and controls, but the interpretation of such differences is not as straightforward as it may seem. We present here a systematic review of the fMRI literature in ADHD; areas covered include executive functions, reward processing, the effects of methylphenidate, comorbidity and spontaneous brain activity in the resting state. To facilitate the interpretation of research in this area, we discuss important conceptual issues, such as the need to take group differences in performance into account or to consider the role of errors. We present common themes that emerge from these studies, and we discuss possible reasons for the many discrepancies that were observed. Finally, based on existing literature and current advancements in fMRI research, we discuss the role that fMRI could play in the future as a diagnostic tool or in treatment outcome predictions, and we make predictions for the future directions of research in this field.

Keywords

Attention deficit hyperactivity disorder; ADHD; functional magnetic resonance imaging; fMRI; children; adolescents; adult ADHD; systematic review; methylphenidate; neuroimaging; resting state

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INTRODUCTION

The development of methods to study human brain structure and function in vivo is one of the great landmarks of medical research. Recent years have seen a proliferation of brain imaging research for the study of the brain mechanisms and pathophysiology involved in psychiatric disorders and associated mental phenomena. There are a number of techniques available each with their own advantages and disadvantages that enable different types of research questions to be investigated. Magnetic resonance imaging (MRI) provides information about structural aspects of the brain, diffusion tensor imaging (DTI) provides information about fibre connections between brain regions, and both positron emission tomography (PET) and single photon emission computed tomography (SPECT) can provide information about regional cerebral blood flow (CBF) as well as neurotransmitter receptor availability. In this review, we focus on the use of functional magnetic resonance imaging (fMRI), the most widely used imaging method in current psychiatric research, and its application to our understanding of brain function in children, adolescents and adults with attention deficit hyperactivity disorder (ADHD).

ADHD is a behavioural syndrome characterised by the presence of developmentally inappropriate levels of hyperactive, impulsive and inattentive behaviours [1]. It is the most common psychiatric disorder in childhood [2] with a worldwide prevalence of around 3-10% [3-5] depending on the criteria applied. The full blown disorder persists in adults in 15% of cases and another 65% show persistence of some symptoms with continued clinical impairments [6]. ADHD is highly heritable with around 76% of phenotypic variance accounted for by genetic influences [7] and molecular genetic studies have identified genetic variants within several genes involved in the regulation of neurotransmitter systems that are associated with increased risk for ADHD [8,9].

For a long time ADHD was thought to emerge from a primary deficit in executive functions (EFs), with an influential theory postulating a specific core deficit in response inhibition [10]. However, Willcutt and colleagues [11] conducted a meta-analysis of 83 studies and showed that although ADHD is associated with weaknesses in response inhibition, working memory, vigilance and planning, such EF deficits were neither necessary nor sufficient for the presence of ADHD. Moreover, Kuntsi and colleagues discuss evidence that shows that impaired performance is often not restricted only to the condition that isolates the cognitive process of interest, suggesting a more general behavioural dysfunction [1]. Furthermore, some studies have shown that performance can improve to normal levels under conditions that are thought to increase arousal and/or motivation, such as the provision of external rewards [12,13] or the faster presentation of stimuli [14]. These findings have rekindled interest in old ideas that were ignored until recently, largely due to the dominance of the EF deficit hypothesis. One theory has postulated a model where performance and attention problems are thought to emanate from a deficit in the regulation of 'energetic state', for example a difficulty in the self-regulation of arousal and the generation and maintenance of the required effort to meet the demands of a task [15]. Another causal model postulates a dual-pathway approach, according to which ADHD may emerge either from a cognitive deficit or from a deficit in reward processing mechanisms [16].

FMRI STUDIES IN ADHD

The use of fMRI in ADHD research has tried to illuminate the neural mechanisms that underlie the behavioural and performance deficits observed in this disorder. In particular the focus has been on the cognitive and neuropsychological mechanisms involved in executive functions such as response inhibition and attentional processes. Yet impairment in ADHD is not restricted to executive functions and deficits in more general processes, such as state

regulation or reward processing, could contribute to it. Recent fMRI studies that have addressed these issues have produced promising results [17-19].

A further potential use of fMRI data is to predict diagnostic status and clinical outcomes, which would require direct comparison with other psychiatric disorders. The development of such 'clinical tests' would not require an understanding of the etiological processes involved, only the existence of robust findings that are sensitive and specific enough to assist in the clinical process. The absence of such data so far suggests that the contribution of fMRI to clinical practice is more likely to emerge from an improved understanding of the neurobiological mechanisms involved. Recent advances in discriminant function analysis of fMRI data [20,21] and the combination of clinical and genetic data might yet generate measures that are sufficiently discriminating for use in clinical practice.

INTERPRETING RESULTS

It must be emphasized that fMRI research is a developing and very complex field and there are few aspects that we can be certain about, especially in the comparison of case-control groups. Every fMRI study appears to show differences in the patterns of brain activation between individuals with ADHD and healthy controls. However, in itself this does not say much. The challenge lies in the interpretation of these differences: what conclusions can we draw about the neurobiology and the etiological processes that underlie ADHD? Unfortunately, the interpretation of fMRI findings, especially from group comparisons, is not as straightforward as it may seem. In the sections that follow, we critically consider the main paradigms that have been used in fMRI research in ADHD, briefly explain the method and discuss some conceptual issues that help in the interpretation of existing research.

RESTING STATE STUDIES

The majority of FMRI studies in ADHD have followed a *task-based* approach, which aims to examine how group status may modulate brain function during the performance of various cognitive tasks. This approach is designed to isolate specific cognitive processes that may be linked to or modified by ADHD symptoms or treatment. Recently however, there has been a re-awakening of interest in an alternative approach that focuses on the *resting state*. The term *resting* is in fact a misnomer since the brain is never at rest [22,23], and is used to denote a task-free paradigm where participants are asked to lie still in the scanner, eyes closed, and are not involved in any specific cognitive tasks.

Resting state paradigms have several potential advantages. They offer a measure of brain neurophysiology that is independent from task-directed cognitive processes. Moreover, the discovery of a "default" mode network of brain structures which are active during the resting state and which show dynamic negative correlations with activity in regions that are task-related is starting to open up new areas of investigation [24,25], raising interesting questions regarding altered patterns of brain activation in patients with ADHD. For example, one question in this area would be to examine the role of such task anti-correlated networks in mediating the effects of motivation on cognitive processes, and how this role might differ between healthy individuals and patients with ADHD.

Resting state studies also have many practical advantages. They are easier to implement, especially with children, and generally they require less experimental time. Therefore they are more cost-effective, given the expense of FMRI research. Potentially a larger number of participants could be tested with the same cost, increasing the power of studies to detect group differences. Adding to this, cognitive studies are associated with greater variability. For example, cognitive studies require the use of a control comparison condition, and subtle variations in this can alter the observed patterns of brain activation [23,26,27]. Therefore, by

avoiding the effects of task variation, resting state paradigms facilitate the comparison of findings across studies. The use of resting state paradigms also avoids the problem of performance differences between groups, which may make the interpretation of group differences more difficult.

Despite these advantages, some authors have questioned the precise contribution that such studies can make in understanding cognitive neurophysiology [28]. Others have argued that the mental processes that are involved are not specified [29]; recently though attempts have been made to illuminate this area [30]. Measurements of brain activity during the resting state have also been associated with increased variability across individuals, which might reflect the unpredictable nature of personal experience during the procedure [29]. Increased variability makes signal detection more difficult. A further criticism correctly indicates that failure to observe, during the resting state, a deficit in brain function does not necessarily mean that the brain is functioning properly when engaged in more demanding cognitive tasks [29]. Yet if a deficit is observed in the resting state despite these difficulties, it becomes all the more interesting as it could suggest a more fundamental neurophysiological dysfunction.

TASK BASED STUDIES

Block versus event-related designs

Task based studies commonly use blood oxygen level dependent (BOLD) signal changes to visualise brain activity (see box 1). There are two main designs for the presentation of stimuli in task based fMRI studies: block and event-related designs. In block designs, stimuli belonging to a particular condition are presented all together in brief epochs (which typically last up to one minute), alternating with epochs representing different conditions or baseline. The recorded BOLD response corresponds to an aggregate of the haemodynamic responses to individual stimuli within the epoch. In event-related designs though, the fast temporal resolution of fMRI relative to some other imaging techniques allows the detection and analysis of the BOLD response to each stimulus separately, providing detailed information on the neuronal response to individual events (see figure 1) [31].

Block designs tend to “maximise power to detect changes in activation while minimising time in the scanner” [32], providing a more efficient way to detect signal changes. However, brain activation during a particular block/condition may reflect a number of different cognitive sub-processes other than the one of interest. For example, response preparation or error related processes might contribute to the activation pattern. Moreover, the repetition of the same type of stimuli within blocks, as well as fixed block orders, make them predictable. This allows for habituation effects and fatigue [29,31]. Finally, the inclusion of errors in block designs is a major concern and will be discussed in more detail below.

In contrast, event-related designs may last longer (more time in the scanner) but they have numerous advantages. A greater scope of analyses is possible, as brain activation in response to particular trial types may be examined, allowing for the isolation of specific cognitive processes in a way that is not possible using block designs. For example, it is possible to look at brain activation patterns corresponding to successful inhibition responses after controlling for stimulus novelty [33], or to analyse the neural correlates for the encoding of stimuli (during an incidental learning task) that were later successfully recognised [17]. Furthermore, event-related designs are less sensitive to motion artefacts and permit the randomisation of the presentation of conditions, as well as the use of variable inter-stimulus intervals, thus combating habituation effects and the predictability of events [31].

Error analysis

One very important advantage of event-related designs is that they allow for the separation of correct and incorrect responses. In block designs, trials with errors are usually analysed together with successful trials. However, Murphy & Garavan [34] have shown that the inclusion of error trials can contaminate the activation signal in two ways: either because the haemodynamic response to error trials is absent or different to that corresponding to successful trials, which represent the cognitive process of interest, or because of post-error processes. Furthermore, a greater number of errors might mean increased levels of frustration, arousal or anxiety [35]. Therefore, if groups differ in error rates, then any group differences in brain activation could be due to contamination effects from errors [34]. To give an example, in a study by Bush and colleagues [36] the ADHD group showed worse performance (including more errors) and engaged a different network of brain regions compared to healthy controls. The authors observed though that the aberrant pattern of brain activation exhibited by the ADHD group corresponded to a network of regions that has been associated with anxiety symptoms across a range of anxiety disorders [36,37].

Event-related designs, by analysing correct trials separately, can isolate activation related to successful performance as well as study error related processes [38,39]. Moreover, neural activation during successful trials can be interpreted in the context of overall task performance, which can provide an index of task difficulty. For example, if the ADHD group shows reduced activation in a particular brain region during successful inhibition trials, and at the same time they show a greater number of errors overall, then this might mean that they found the task more difficult and the increased task difficulty could be associated with the hypoactivation in the particular region. Some studies have examined such hypotheses by calculating the correlations between BOLD signal changes in a particular area and number of errors, yielding contradictory results [35,40]. Alternative explanations are possible though: for example, the ADHD group might have been less engaged in the task. Thus, caution should be exercised in drawing inferences. Moreover, even in event-related designs, signal contamination effects from post-error processes could still remain. Finally, even though event-related designs may avoid the problem of performance differences between the groups in terms of errors, there are still other aspects of behaviour where a group match is usually not achieved, such as reaction times and intra-subject variability. The issue of performance differences though is discussed in the section that follows.

Taking performance into account

Taking task performance into account is of particular importance in block design studies, where one cannot isolate and study correct trials separately. Especially when comparing a healthy group to a clinical group, one needs to make sure that the clinical group can perform the task [41]. If patients cannot perform the task, or if patients cannot get engaged to perform the task, then the neural systems that underlie the task-related cognitive processes cannot get involved. In that case, any interpretation of group differences in brain activation would be mere speculation. Fortunately, this does not seem to have been a problem in most of the studies reviewed here, with only one exception [42].

If patients can perform the task but show impaired performance, then it is *not* possible to ascertain if any group differences in brain activation are the cause of the impaired performance (e.g. representing a local structural or functional abnormality), or the result of the decrement in behavioural performance. This approach though is likely to identify areas of the brain that are involved in the performance of a task overall [41,43]. Further evidence, e.g. from other imaging modalities or from animal studies could help to disentangle the direction of causality. This point is of particular relevance to the block design studies

reviewed in this paper. We examined group differences in behavioural performance in all of them and in most cases found that although they are reported as non-significant, in fact they corresponded to large effect sizes. Apparently, due to the small sample sizes (ranging in most block design studies from 8-12 participants per group), the studies did not have sufficient power to detect even such large effect size differences as significant. We calculated effect sizes for all studies where data was available and confirmed that their power was insufficient. Therefore, we would strongly suggest that underpowered fMRI studies take into account real group differences in behavioural performance (estimated with effect sizes) when interpreting imaging results.

When clinical and healthy groups show equivalent task performance, the lack of activation by the ADHD group of brain regions that form part of a network that is normally activated by healthy participants during the task suggests that these regions might not be necessary for task performance (providing there is no overactivity in other neuronal systems) [41,43]. If, in the presence of equivalent performance, the ADHD group seems to employ new areas, this could suggest the use of new cognitive strategies, or the presence of degeneracy. The concept of degeneracy refers to the existence of multiple neural systems that can perform a function which is usually performed by a single system that inhibits the rest [44]. Ideally, the attribution of abnormality should not be based solely on group status. To explain, if two groups perform a task equally well but one shows reduced activity in related brain areas, this might imply greater neural efficiency. Indeed, in a number of research studies that have examined the effects of polymorphisms in genes involved in the dopaminergic system (and which are associated with risk for schizophrenia) on prefrontal activity during working memory tasks, the advantageous alleles were associated with increased neural efficiency, that is more focused activation (or increased signal to noise ratio in the prefrontal cortex) during working memory tasks and improved performance [45-47]. A further aspect that should be specified is whether group differences reflect the amplitude of BOLD signal changes at specific sites, the extent/volume of the activated areas, or both [27,48,49]. In any case, the presence of group differences in brain activation in the absence of performance differences suggests that neural activity changes, measured with BOLD fMRI, are a more sensitive index of abnormality in ADHD.

Systematic Literature review

To provide a systematic review of the literature we searched the PubMed (www.pubmed.com) and the Web Of Knowledge (<http://portal.isiknowledge.com>) databases using the following keywords: “ADHD”, “attention deficit hyperactivity disorder”, “ADD”, “inattention disorder”, “hyperactivity disorder”, “hyperkinetic disorder”, “attention deficit disorder”, “fMRI”, “MRI”, “functional magnetic resonance imaging” and “magnetic resonance imaging”. We also searched the reference lists from identified articles for relevant studies. The search included all years and was completed up to March 2007. One additional study that was in press was provided by Dr Katya Rubia [50]. The search was restricted to publications written in English and included all papers that reported on fMRI data and participants with ADHD. The overall quality of the studies was satisfactory, particularly of the more recent studies that in most cases used groups that were matched for IQ and age and used standardised diagnostic procedures. The small sample sizes though are a cause of concern due to the reduced power to detect significant differences [51]. All the studies used children and adolescents, except for two studies that used adults [36,52]. Although there is a tendency in the literature to use the term ‘hyperactivity’ interchangeably with ADHD, when we mention in the text ‘hyperactivity’ we refer specifically to this subcomponent of the disorder and not to the full syndrome.

We excluded two studies from this review. The first is a study by Zang and colleagues [49] because the operationalization of cognitive interference did not appear to work with the

ADHD group, and no statistical test was conducted to examine group differences for the obtained brain activation volumes. We concluded that we could not make meaningful interpretations due to these limitations. The second was a study by Sunshine and colleagues [53]. This is in fact the earliest study that we identified, which used an fMRI block design to study brain function in ADHD, but they did not include a control group. This paper did however generate some important questions that were addressed in later research, such as the idea of compensatory networks [54], and the idea to use tasks that can reliably elicit strong neural activation so as to facilitate group distinction and analysis at the single subject level [36,55].

TASK-BASED STUDIES OF COGNITIVE PROCESSES

In this section we review studies that have examined how group status may modulate brain function during the performance of various cognitive tasks. We only report brain activation differences between ADHD and control groups *if they were shown to be significant in direct between-group statistical comparisons*. Often, within-group analyses showed that certain brain regions were activated in one group but not in another when particular contrasts were examined. However, an area may have shown activation in one group because it just reached the statistical threshold, but may not have shown activation in the other group because it fell just short of the required threshold. The only way to be certain that an observed difference between two groups is significant is to conduct direct statistical tests comparing the groups.

Inhibitory control

The majority of task-based fMRI studies in ADHD research have used experimental designs that tap different aspects of executive functions, mostly inhibitory control [26,27,32,33,35,36,38-40,56-62]. This is not surprising; poor inhibitory control is a central feature of impulsiveness and is commonly observed to be impaired in ADHD [11,63]. Studies have investigated different aspects of inhibitory control including withholding of a prepotent response (typically using the Go/No Go task), the suppression of a response that may have already started (typically using the stop task), or the protection from cognitive interference (usually using different versions of the Stroop task). In the following section we discuss these studies, examining block and event-related designs separately.

Block design studies—Three block design studies examined neural function during inhibitory control tasks in children and adults with ADHD and found evidence for reduced frontal and striatal activity. Rubia and colleagues [59] reported reduced activation in the ADHD group in mesial and lateral prefrontal areas in the right hemisphere and in the left caudate. Booth and colleagues [26] found that the ADHD group showed decreased activation in a widespread network of frontal regions, predominantly in the right hemisphere, including regions in the ventrolateral (VLPFC) and dorsolateral prefrontal cortex (DLPFC), the mesial prefrontal cortex (mPFC) and the anterior cingulate cortex (ACC). Moreover, reduced activation was also observed in the striatum, amygdala and thalamus, as well as the fusiform gyrus (FG) and the mesial inferior parietal lobe (mIPL).

Bush and colleagues [36] focused on the dorsal ACC (dACC). They explained that this region is thought to subserve the cognitive-attentional processes of stimulus and response selection, including the facilitation of correct and inhibition of incorrect responses, adding that a deficit in these processes could partially account for the impulsivity and inattention problems observed in ADHD. They found that an adult group of ADHD patients showed reduced activation in the dACC during the cognitive interference control condition of the counting Stroop task [64].

In these studies the authors failed to find significant group differences in measures of task performance. However, when we calculated the effect sizes for the reported group differences a different picture emerged, as in all studies the ADHD group showed substantially worse performance. To give an example, in the study by Bush and colleagues [36] the group difference in one of the behavioural measures had a large effect size (Cohen's $d=0.73$), while the power of the study to detect this difference was only 28%. This indicates that we cannot safely rely on non-significance to discount performance differences. The observed frontal and striatal hypofunction might therefore result from either reduced engagement with the task, impaired performance, or error related activation and post-error processes, rather than indicate the cause of impaired task performance.

In another study by Vaidya and colleagues, brain activation patterns seemed to be task specific [27]. They used two versions of the Go/No Go task, where conditions were matched either in terms of stimulus content (stimulus-controlled condition) or in terms of the number of responses (response-controlled condition). They found that the ADHD group showed less extensive striatal activation in the stimulus-controlled task, whereas they showed greater frontal activation in the response-controlled task. In both tasks, the ADHD group showed worse performance. This study shows that the choice of control condition is crucial (see also [26]). The underactivation of the striatum is consistent with other block design studies reported here [26,59]. Its presence only in the stimulus-controlled task perhaps reflects the fact that response inhibition was rarer and therefore more difficult in this task (compared to the response-controlled task). However, reduced striatal activation has also been observed in studies where inhibition was relatively easy [59]. An alternative explanation is that striatal activation could be related to differences in motor activity between the conditions. The observation of frontal hyperactivation in the response-controlled task in the ADHD group was later replicated in a study by Schulz and colleagues [32].

Schulz and colleagues used a group of adolescents who had been diagnosed with ADHD in childhood, half of whom currently met the DSM-IV criteria for ADHD in partial remission [65] while half met the criteria for the full diagnosis [32]. Interestingly, in the absence of any group differences between the ADHD cases and controls in behavioural performance during tasks that tapped cognitive interference control and response inhibition, the ADHD group showed *increased* activation in the VLPFC, the DLPFC, the ACC and the striatum. They found that activation in these areas strongly correlated with the level of inattention and suggested that the increased and more widespread prefrontal activation in the ADHD group might reflect the need for greater 'cognitive effort' to achieve comparable performance with the healthy group.

Event-related design studies—Schulz and colleagues provided further support for their findings of increased frontal activity in adolescents with a childhood diagnosis of ADHD using event-related designs [40,61]. In the first study [40] successful inhibition was associated with *increased* activity in an extended network of frontal (including the dACC) and parietal areas for the clinical group, while at the same time *decreased* activation was observed in the temporal cortex and the hippocampus, the occipital cortex, the precentral gyrus and the cerebellum. Moreover, activation in the ACC was positively correlated with error rate for both groups. Going a step further, Schulz and colleagues [61] found that the above *increases* in inferior prefrontal and parietal activation, and *decreases* in occipital activation followed a linear *trend* depending on ADHD status. For the participants with a current diagnosis of ADHD in partial remission, activity in these areas was midway between that of healthy controls and those with a current full diagnosis of ADHD, and exactly the same linear *trend* was found for differences in accuracy. This pattern of findings weakens the argument that the observed hyperactivation, which was inconsistent with findings in

other studies, could have been due to the ‘partial remission’ status of half of the sample [32,40].

In a study that used adolescents with a *current* diagnosis of ADHD, Pliszka and colleagues also found increased activation in the ACC during successful inhibition trials [38]. However, when they examined inhibition errors, they found reduced activation in the ACC for the clinical group. In the right DLPFC, the ADHD group showed increased activation irrespective of trial type. Behaviourally, the ADHD group showed substantially different (but non-significant) effect sizes with more impaired performance but faster reaction times than the comparison group. The association of inhibition errors with a reduction in ACC activity raises concerns about the validity of block design studies which include errors in the analysis and report hypoactivation in the same region, given that the ADHD groups made a substantially greater number of errors [26,36,59]. In the only other study that examined inhibition errors, using a similar (stop) task, Rubia and colleagues [39] failed to replicate the finding of decreased activity in the ACC, but instead found that the clinical group showed decreased activation in the posterior part of the cingulate cortex (PCC) and the mesial parietal lobe, which was negatively correlated with ADHD symptom severity.

Three further studies, using the largest clinical groups (14 to 19 cases) among event-related studies, provide evidence to support the hypothesis for hypoactivation in frontal-striatal networks in ADHD [39,58,62]. However, there are large inconsistencies in the exact areas involved and in laterality. Rubia and colleagues [39] found that successful inhibition was associated with reduced activation in the right VLPFC and superior temporal cortex in the ADHD group, while activity in the right VLPFC correlated negatively with ADHD symptom scores. Although success of inhibition was matched between the groups, performance differed since the ADHD group showed substantially higher intrasubject variability and omission errors. Using the same ADHD sample, Smith and colleagues [62] found reduced left prefrontal activation using a different task. They also used a *switch task* to examine brain activation during trials where the participants had to inhibit a learned stimulus-response association and learn a new one; they found reduced activation in bilateral temporal cortex regions in the ADHD group. In this study, although group differences in task performance disappeared when age was used as a covariate, age did not have an effect on the imaging results. In another study Konrad and colleagues [58], using a cognitive interference task, found decreased activity in the left primary motor cortex and the right putamen, while they observed increased activation in the left mesial parietal cortex; this pattern was maintained even when they compared groups matched on performance (the ADHD group showed slower reaction times and made more errors). A negative correlation was also observed between signal change at the putamen and hyperactivity/impulsivity symptom severity (see also [66]).

Further support for the hypofrontality hypothesis came from a study by Vaidya and colleagues which used a task tapping two different aspects of inhibitory control [35]. In the context of impaired accuracy, the ADHD group showed reduced activation in the left VLPFC and the right inferior parietal cortex during the interference control condition, while in the response inhibition condition they showed decreased activity in the right VLPFC and the primary motor cortex. For the ADHD group, improved performance correlated with activation in the VLPFC and the medial parietal lobe in the interference control task and the right temporal cortex in the response inhibition task. For the healthy comparison group it correlated with activation in frontal regions and the caudate for both tasks.

Tamm and colleagues [33] (and later Smith and colleagues, see [62]) modified a Go/No Go task so as to account for the novelty (and thus increased salience) of the infrequent No Go trials. The ADHD group again showed reduced frontal activation, mainly in the ACC, while

they showed increased activation over the temporal cortex. Behaviourally, the ADHD group committed more accuracy errors.

Finally, two further studies by Durston and colleagues used event-related designs that manipulated task difficulty [56,57]. In the first study [57], the ADHD group showed reduced accuracy overall, with the number of errors increasing as a function of preceding Go trials for both the control ($r=.90$) and ADHD ($r=.79$) groups. During successful inhibition trials, the ADHD group showed *decreased* activation in the left caudate and *increased* activation in the DLPFC, the PCC, and regions in the parietal, temporal and occipital cortices. However, when they repeated the same set of analyses in a second sample [56], the results were largely in the opposite direction. Performing a region of interest analysis, they found that the ADHD group showed *decreased* activation in the left VLPFC and the right DLPFC, the ACC and the inferior parietal lobe, while they did not show increased activity in any region. Moreover, there was no involvement of the striatum. The inconsistencies in the studies by Durston and colleagues, who used the same task but different samples, and in the studies by Rubia, Smith and colleagues, who used the same sample on related tasks, raise questions about the reliability and replicability of fMRI findings, which have rarely been tested [51].

Durston and colleagues [56] also included a group of unaffected siblings of the ADHD probands to investigate whether prefrontal activation during inhibitory control could be used to index the familial risk associated with ADHD. As expected from a familial disorder, the accuracy of response for the sibling group fell between the ADHD and the healthy groups. Although there were no significant group differences in brain activation between siblings and ADHD probands during successful inhibition trials, the siblings showed reduced activation at frontal and parietal regions compared to the healthy control group, showing that brain activation during inhibition was more similar to that of their affected siblings. What is very interesting to note, especially for the purposes of using fMRI to differentiate between groups, is that there was no overlap in BOLD signal change in the right inferior frontal gyrus between the control group and the sibling groups. Overall these observations indicate a lack of sensitivity of the BOLD signal to diagnostic status although it may be more useful as a neurobiological index of underlying familial (and likely genetic) susceptibility.

Effects of long-term treatment

The importance of studying patients who have never received stimulant treatment lies in being able to interpret the observed activation patterns as an intrinsic feature of the pathophysiology of the disorder rather than as an outcome of the effects of long term medication treatment on the brain [39]. To address this issue recent studies have attempted to include as many children as possible that have never received stimulant medication [17,18,56,67], and a few have managed to use samples that are fully medication naïve [38,39,42,58,62].

These studies suggest that altered brain activation patterns in children with ADHD are not due to the effects of long term stimulant treatment. The best design though that could examine the effects of long term stimulant treatment on brain function in ADHD would be one that includes both a treatment naïve sample and a sample that has received long term medication, alongside a healthy comparison group. Such a study was carried out by Pliszka and colleagues [38], using a response inhibition (stop) task. On almost all comparisons, they failed to find significant differences in brain activation or behaviour between drug naïve and long term treated ADHD groups (the latter were off medication during testing for a minimum of 24 hours). In the few cases where there were differences the ADHD group who had received long term treatment was closer to the healthy comparison group. Therefore, this study suggests that if there is any effect of long term stimulant treatment, it acts in the direction of normalising neural function.

Studies on attentional processes

All of the above *response inhibition* paradigms unavoidably engage attentional processes in one form or another. For example, Go/No Go tasks involve sustained attention and alertness while Stroop-like tasks involve selective attention too. In most studies, impaired performance for the ADHD group was not limited to the conditions that isolated some aspect of inhibitory control, but was also observed in baseline conditions. Kuntsi and colleagues [1] discuss cognitive studies that confirm the presence of a more generalised behavioural deficit that cannot be fully explained by a deficit in inhibitory control processes. To address problems of inattentiveness, which is a defining feature of ADHD, some fMRI studies have used tasks that target different aspects of the attentional system [26,50,58,67,68].

Booth and colleagues [26], in a block design study, used a visual search task to study brain function during selective attention. Using two different baseline comparison conditions, they found significant group differences only when the selective attention and baseline conditions matched in terms of visual load. The ADHD group showed decreased activation in temporal and parietal regions. This demonstrates once more the importance of selecting an appropriate baseline condition that controls for all possible confounding factors (see also [23,27]).

Shafritz and colleagues [68] conducted a block design study using a group of cognitive tasks that examined selective visual, auditory and divided attention. In the visual attention task performance did not differ between the ADHD and healthy groups, but in both the auditory attention and divided attention tasks the ADHD group performed worse than controls. They found decreased activation in the temporal cortex in the auditory selective attention task in cases compared to controls. In addition, the left dorsal striatum was only engaged in the more cognitively demanding divided attention task, during which the ADHD group showed decreased activity compared to controls (a similar task specificity for striatal activity was seen in [27]).

Konrad and colleagues [58] studied different aspects of attentional functions using a task condition with cues that signalled upcoming stimuli and another condition that required the disengagement of attention from peripheral stimuli. The ADHD group made more errors in both conditions and showed slower reaction times in the reorienting condition. In the 'alertness'/motor preparation condition, the ADHD group showed decreased activation in the right ACC, while they showed increased activation in the brainstem. In the reorienting condition, the ADHD group showed increased activation in the right putamen and the right VLPFC, which persisted even when subgroups of equivalent performance were compared. Moreover, there was a strong and significant inverse relationship between putamen signal change and hyperactivity/impulsivity symptom severity in the reorienting condition ($r = -.80$). The association of putamen function with levels of hyperactivity is consistent with findings reported in a study by Teicher and colleagues [66] discussed later.

Tamm and colleagues [67] and Rubia and colleagues [50] both looked at brain function during detection of infrequent (oddball) visual stimuli. In the first study [67], while performing more omission errors, the ADHD group showed reduced activation bilaterally in the parietal cortex, the right precuneus and the thalamus. Moreover, the number of voxels activated in the left inferior parietal cortex was inversely related to the number of commission errors ($r = -.52$, $p < .05$). The finding of more commission errors both when the inhibition of a prepotent response was required (to the oddball stimuli) but also when the frequent stimuli reappeared right after the oddball stimuli suggests that there might be a fundamental problem in attentional/response shift. This pattern cannot be fully explained by a response inhibition deficit, which would predict response errors only to the oddball stimuli

[67]. Rubia and colleagues [50], with a paradigm that did not require a different response to the infrequent stimuli, found that the ADHD group showed decreased activation in the temporal and left inferior parietal cortices, the PCC, as well as in the insula, striatum and the thalamus.

Working memory

Valera and colleagues [52] have conducted the only fMRI study (block design), to our knowledge, that examined the functional neuroanatomy of working memory, using the N-back task and employing the largest ADHD group (n=20) among task-based studies. In the absence of any behavioural differences in accuracy, reaction times or reaction time variability, they found that the ADHD group showed less activation in the left posterior lobe of the cerebellum, the left inferior occipital gyrus, and a trend for less activation in the right PFC. However, only the difference in the cerebellum remained significant when participants with learning disabilities were excluded (without any significant effect on behavioural performance). Although functional abnormalities in the cerebellum have not been often observed in fMRI research, this might be due to the choice of tasks (e.g. see [69] for a task-free paradigm), as well as to some technical choices/limitations especially in earlier studies, where parts of the cerebellum were excluded from imaging. The cerebellum, particularly the posterior inferior vermis, are among the areas that were found in a recent meta-analysis of structural imaging studies to show the greatest and most significant area of volumetric reductions [70] in youths with ADHD.

Mental rotation

Silk and colleagues [42], in a block design study, compared a group of medication naïve adolescents with ADHD to a group of healthy controls on a mental rotation task, in which participants had to match a target shape to one of four rotated shapes. The authors found significant group differences in brain activation, with the ADHD group showing decreased activation in a wide network of cortical regions and in the caudate, while they showed increased activity in the temporal lobe, the PCC and the mPFC. Yet they also found that the ADHD group performed at *chance* levels (27% success rate versus 56% for the healthy control group). Therefore, these data suggest that either the ADHD group could not perform the task or that they did not really engage in the task. In the presence of such marked behavioural differences, a clear interpretation of the brain activation differences observed is difficult.

A quantitative meta-analytic approach

In an attempt to provide a robust summary of available fMRI studies Dickstein and colleagues [71] performed a quantitative meta-analysis of task-based imaging studies in ADHD using 13 fMRI [26,32,33,35,36,38-40,42,52,57,62,67] and 4 PET/SPECT studies that had published 3-D stereotactic space coordinates. The authors concluded that the meta-analysis produced objective, unbiased and statistically based evidence that demonstrated the existence of hypoactivity in ADHD across a wide network of regions. They made the important point that the extent of the neural networks remains uncertain since the available data were limited by the narrow selection of the tasks employed in the studies included in the analysis, almost all of which targeted executive functions.

The meta-analytic data showed reduced activation in regions in the left PFC, the ACC, the right parietal lobe, the occipital cortex and in the thalamus and claustrum. When only response inhibition studies were included in the analysis, a more restricted network was identified which included the right caudate. The analysis also identified certain regions where the ADHD groups tended to show hyperactivation: these included parts of the left PFC, the left thalamus and the right paracentral lobule.

Although this quantitative approach is promising and enables combination of data across multiple datasets, a major limitation was the small number of suitable datasets, as well as the unavoidable inclusion of studies that were quite dissimilar in the specific aspects of their design and quality. For example, in the study by Silk and colleagues [42] where the ADHD group appeared to perform at chance level, the observed hypofrontality might have been totally different in origin from that observed in an event-related study where only correct trials were analysed. Analysing these two studies together on an equal footing strengthens the hypoactivation argument, yet is based on evidence of questionable validity. Therefore, future meta-analyses of studies that use clinical groups should ideally be stricter in their criteria for inclusion of studies, taking into account overall quality as well as making sure that there is sufficient evidence to show that the clinical group can perform the task or has engaged in the task [41].

BEYOND EXECUTIVE FUNCTIONS

It is only recently that ADHD researchers have ventured outside the domain of executive functions with two papers that were published in 2007 [17,18]. The evidence that more general processes are likely to be disrupted in ADHD and could underlie observed performance deficits in executive functions make this line of enquiry highly important. Both studies used fMRI to examine brain processes that are thought to be mediated by dopaminergic activity [72]. Scheres and colleagues [18] decided to explore alternative processes that may lead to ADHD, namely, the function of reward processing and motivation mechanisms. They found that during a task that involved reward anticipation the ADHD group showed reduced activation in the right ventral striatum, with similar findings reported for the left ventral striatum. There was also a significant interaction between group status and reward value, with no overlap in striatal activity between the groups only for the highest monetary value. Activity in the ventral striatum appeared to show a linear relationship with the value of the expected reward, similarly to that seen in other studies with healthy adolescents and adults [73,74]. Moreover, hyperactivity/impulsivity scores showed a moderate negative correlation with ventral striatal activity levels. One possible explanation for this finding is that a dysfunction in dopamine based reward mechanisms leads to reduced salience of anticipated rewards in ADHD.

Krauel and colleagues [17] manipulated salience (using pictures that were either neutral or had high emotional content) in an incidental learning task. They examined whether increasing salience enhanced recognition and modulated neural processing during the encoding of the successfully recognised pictures. The ADHD group showed impaired recognition performance only for the neutral pictures. Moreover, during the encoding of the successfully recognised neutral pictures the ADHD group showed decreased activity in the left ventral ACC but increased activation in the left superior parietal lobe/precuneus, the right insula and superior temporal, occipital and left middle frontal gyri. During the encoding of successfully recognised emotional pictures the ADHD group showed increased activity in lateral and medial regions of the right parietal cortex.

Both studies [17,18] provide evidence for a dysfunction in reward processing and motivational neural networks in ADHD (ventral striatum – ventral ACC) and pave the way for more functional neuroimaging studies to investigate these mechanisms as well as their interaction with cognitive functions, such as episodic memory.

STUDIES OF MOTOR FUNCTION

Some studies have supported the existence of a core motor deficit in ADHD [75], and two studies have used fMRI to study motor timing and performance. Rubia and colleagues [59] used a motor timing task where participants had to tap their finger in line with a tone

appearing either at short or long intervals. In the long interval condition (compared to the short interval condition), the ADHD group showed decreased activation in the ACC and the PCC, but increased activity in the supplementary motor area (SMA) compared to controls. They also showed substantially (but not significantly) reduced performance, with higher mean synchronisation time and response time variability. However, when looking at the short interval condition (compared to the long interval condition), no significant group differences in brain activation were found [60]. Rubia and colleagues [50] also looked at brain activation during a simple choice reaction time task and found that the ADHD group showed reduced activation in the right ACC and mesial PFC and the right DLPFC. The effects of motor performance on brain activation should be examined more carefully in response inhibition tasks, as the contrasted conditions are not matched in terms of required motor responses, while the study by Vaidya and colleagues [27] has suggested that this may be an important factor to consider.

Mostofsky and colleagues [48] examined brain activation during a simple sequential motor tapping task. They wanted to find the neural correlates of motor flow abnormalities in ADHD. This refers to involuntary movement in the homologous muscles in the opposite side of the body during voluntary activity [76], and is thought to be a reflection of a more general failure of inhibition. It is commonly observed in pre-school children, who grow out of it by the time they go to school, while children with ADHD seem to show it for longer, perhaps indicating a developmental delay. In children with ADHD motor flow abnormalities have also been shown to predict response inhibition performance [77]. Mostofsky and colleagues measured motor function outside the scanner with a neurological examination, but they observed only a general and subtle impairment in motor function, while in the scanner both ADHD and control groups showed similar tapping performance. The ADHD group showed decreased activation in the right superior parietal cortex, and activated a smaller area of the contralateral primary motor cortex.

This is an example of a study where brain activation differences cannot be interpreted in the absence of behavioural differences, inside or outside the scanner. Different activation patterns cannot be associated with motor flow abnormalities as there were no apparent group differences in this domain. In the absence of impairment, reduced brain activation could even be interpreted as increased neural efficiency. What this study has shown is that children with ADHD show differences in brain activation in areas related to the performance of patterned movements, which could be related to unmeasured task performance differences or to the subtle motor performance deficits that were observed off-line.

ADHD AND COMORBID DISORDERS

The association of ADHD with co-morbid disorders has yet to be widely investigated using fMRI paradigms. However one area that has started to be addressed is the controversial link between ADHD and juvenile bipolar affective disorder (BD), both of which share similar problems with impulse control. Two studies examined differences in brain function between groups of youths with BD with or without comorbid ADHD. Adler and colleagues [78] used a simple attention task in a block design study and found that, in the absence of performance differences, the comorbid ADHD+BD group showed increased posterior parietal and decreased PFC activity compared to the group with BD only. In the other study Leibenluft and colleagues [79] used a stop task in an event-related design and found that the comorbid ADHD+BD group showed increased activity in the right putamen and ACC compared to both a healthy comparison group and the BD only group, in the successful-unsuccessful inhibition contrast. When they examined error trials, there were no differences between the two clinical groups but they both showed reduced activation in the striatum, and the comorbid group also showed reduced activation in the VLPFC and the ACC, compared to

the healthy group. These findings show that the presence of comorbid ADHD+BD might be associated with different patterns of neural activation than those observed in BD alone. However, these studies are very preliminary, since the lack of a healthy comparison group in the study by Adler and colleagues [78] or of an ADHD only group in both studies does not allow the dissociation of functional abnormalities associated with each of the disorders separately.

Another area of interest is comorbidity with reading difficulties (RD), since twin studies have shown that there is a substantial degree of overlapping genetic influences between ADHD and RD [80,81]. Shafritz and colleagues [68] compared a group with RD and a group with ADHD with the purpose of examining whether the neural correlates of attention deficits in ADHD and the modulating effects of methylphenidate (MPH) are shared between related neurodevelopmental processes. This study showed that there are commonalities in the neural deficiencies during attention tasks between ADHD and RD groups, as well as that MPH has a similar mode of action and similar effects in both groups (see below for more details). Interestingly, twin studies have shown that the correlation between RD and inattention, but not hyperactivity/impulsivity symptoms, is due almost exclusively to common genetic effects [80,81], and future studies should examine whether common neural deficiencies between ADHD and RD are also observed during processes other than attention.

USING FMRI TO STUDY THERAPEUTIC EFFECTS

FMRI studies have also been used to examine the effects of acute stimulant treatment (methylphenidate – MPH) on task-related brain function [27,49,68], as well as the effects of extended stimulant treatment (1-4 weeks) on resting state brain function [66,69]. Another use has been the investigation of the effects of extended neuro-biofeedback therapy on task related performance and brain activation [82,83].

Two task-based studies suggest that the effects of MPH on brain activation are task and region specific. Shafritz and colleagues [68] used a placebo-controlled, double-blind design to examine the modulating effects of MPH on brain activation during attentional processes in ADHD (the study has been described in more detail in the section on attentional processes). MPH did not have any effects on behavioural results, but it modulated striatal activation in the divided attention task only. Although the ADHD group had shown decreased activation in the left dorsal striatum compared to the healthy control group while they were off medication, the difference disappeared in the MPH condition. The second study by Vaidya and colleagues [27] used MPH on a healthy as well as the ADHD group. Participants were tested on two occasions one week apart, on or off MPH. While off MPH, the ADHD group showed reduced striatal activation in the stimulus-controlled task, while showing increased frontal activation in the response-controlled task (details of the study and the findings from group comparisons while off medication were discussed in the section on inhibitory control). In the stimulus-controlled condition, the administration of MPH improved performance and increased frontal activation for both groups. Yet the pattern of striatal activation was reversed: activation was increased in the ADHD group and decreased in the control group, so that now the ADHD group activated a greater area of the striatum than the comparison group. In the response-controlled task MPH improved performance in the ADHD group but had no detectable effect on brain activation. The authors also conducted an analysis at the single subject level and found that group differences were driven by eight out of ten participants with ADHD and five out of six healthy control participants showing the characteristic response in the striatum. This underlines the ability of fMRI to produce reliable results at the single subject level and the potential clinical utility of pharmacological challenge studies.

Until recently, the acquisition of quantitative measures of cerebral blood flow was only possible with PET/SPECT. However, the development of arterial spin labelling [84] has enabled similar measures to be derived using fMRI. T2 relaxometry is another relatively new technique which has been shown to assess blood volume during steady states indirectly [85], with a high T2 relaxation time (T2RT) corresponding to reduced blood volume. Two further studies using this technique suggest that the effects of MPH depend on baseline levels of activity.

Teicher and colleagues [66] examined specifically the effects of MPH on the striatum in a triple-blind, randomized, placebo-controlled study, using T2RT to evaluate blood volume. They examined striatal T2RT while participants were simply lying still ('resting') in the scanner. Beforehand, they had obtained objective measures of motor activity using an infrared camera, during the performance of a response inhibition and an attentional task outside the scanner. When tested off MPH, they found that the ADHD group showed decreased blood volume in the left putamen. In the tasks performed outside the scanner, MPH improved task performance and reduced variability and motor overactivity. An interaction between the effects of MPH and baseline activity levels (off MPH) was also noted. Interestingly, treatment with MPH led to increased blood volume in the left putamen for the most hyperactive children, while it had the opposite effect for the least hyperactive children. A similar effect was also found for the right caudate. The authors argued that the involvement of the putamen is meaningful since it is mostly involved in motor activity, while the anterior caudate is involved in higher cognitive functions. These findings bear remarkable similarity to those from Vaidya and colleagues [27], confirming that region specific effects of MPH are dependent on baseline levels of motor activity.

In a similar triple-blind, randomized, placebo-controlled study by the same group the focus was shifted to the effects of different MPH doses on blood volume in the cerebellum [69]. The cerebellar vermis is one of the main brain structures that has been shown to have reduced volume in ADHD [70] and is also known to contain a substantial density of dopamine transporters [86-88]. As in the previous studies, they found that the effects of MPH depended on baseline motor activity levels. For the most hyperactive boys MPH treatment led to reduced blood volume in the cerebellar vermis, whereas for the least hyperactive boys they observed an increase in blood volume. The direction of blood volume changes in the cerebellum are in the opposite direction to those seen in studies of the striatum [66] where MPH treatment of the most hyperactive children led to increased blood volume.

More recently Beauregard and Levesque [82] randomly divided a group of children with ADHD into two subgroups, one receiving a 14-week neuro-biofeedback treatment and an untreated control group. They used a blocked counting Stroop task [64] and an event-related Go/No Go task before and after treatment. Prior to treatment there were no group differences, whereas in the treatment group after the 14-week period the cognitive interference task was associated with increased activation of the right ACC, the left caudate and the left substantia nigra and the response inhibition task was further associated with increased activation in the right VLPFC and left thalamus. Performance also improved for both tasks. These findings are consistent with the hypothesis that links hypoactivation in a frontal-striatal network with impaired inhibitory control performance in ADHD, although they cannot disentangle the direction of causality. The increased activation in the striatum and the substantia nigra after treatment may suggest that the effects were mediated by increased dopamine activity.

RESTING STATE STUDIES

Resting state studies in ADHD have investigated regional neural activity [89,90], the effects of MPH on an indirect index of cerebral blood volume (discussed above) [66,69], differences in the functional connectivity between regions [19] or have used pattern recognition analysis to discriminate between groups [21]. The methods for analysing resting state data are still at an early stage of development and further research must establish the relationship between obtained measures and brain physiology.

Cao and colleagues [89] used regional homogeneity analysis, a technique that maps brain function by looking at the synchrony in BOLD signal low frequency fluctuations (LFFs) among neighbouring voxels across time [21]. They found that the ADHD group showed reduced regional homogeneity in the VLPFC, the right ACC, the left caudate, the left precuneus and the cerebellum. These areas have shown dysfunction in ADHD in many of the studies discussed above. The ADHD group also showed increased regional homogeneity in the lingual gyrus, cuneus and left parahippocampal gyrus. Zang and colleagues [90] also found significant decreases in the *amplitude* of BOLD low frequency fluctuations (ALFFs) in the right VLPFC and the cerebellum, and increases in the right ACC and loci in the temporal and motor cortices, the cerebellum and the midbrain. The authors explain that this neurophysiologic index (ALFF) is thought to represent spontaneous neuronal activity, although this link has not been specifically addressed in research.

Zhu and colleagues [21] used a multivariate statistical technique that has recently attracted a lot of interest in the analysis of brain imaging data [20,91]. Essentially, if we suspect that we have two different classes of data (corresponding to two different mental states or disorders), pattern recognition analysis finds that function that best discriminates between our states or groups. Zhu and colleagues [21] constructed regional homogeneity maps for an ADHD and a healthy control group using a resting state paradigm and found that their model could correctly predict status for 91% of controls and 78% of ADHD cases. The group also found that applying the same group discrimination analysis method to structural imaging data in their study was not useful, suggesting that functional imaging data may be more sensitive to ADHD. They further found that the regional homogeneity data from the prefrontal cortex and the ACC were best for discriminating between the two groups. This therefore also provided further evidence for the core role of a functional impairment of the prefrontal cortex and the ACC in ADHD. Although not yet used in other types of studies, this analytical approach is promising since it can also be applied to other fMRI paradigms, such as the block design studies described previously.

Finally, Tian and colleagues [19] used another method, functional connectivity analysis, that looks at the temporal correlation in BOLD signal changes between different regions of the brain. They used this method to examine the functional integration of the dorsal ACC with other brain regions. They found that in the ADHD group compared to controls, the dorsal ACC showed stronger functional connectivity in the resting state with a number of other brain regions, all of which have been linked to some role in autonomic system function and control (thalamus, cerebellum, insula and pons). This finding is in line with a postulated deficit in self-regulation of arousal in ADHD [15] and further illuminates the potentially important role of non-executive processes in producing the observed disruption of higher executive processes. For example, although the ACC has often been implicated in the studies that employed executive function tasks, it has in fact been shown that it is not an essential part of a cognitive control network [92] and has been found to be involved in task-related autonomic control [93]. Both Tian and Critchley argue that the involvement of the ACC in emotional and executive tasks might be due its role in the regulation of state arousal to meet current behavioural demands.

POTENTIAL USE OF fMRI IN CLINICAL PRACTICE

We have seen that fMRI research has been used to examine both pharmacological and behavioural treatment effects and could also be used to examine the pre-treatment neural correlates of later successful treatment outcomes. In this way, fMRI might become a useful tool in the prediction of the likely effectiveness of stimulant treatment.

On a second front, fMRI could potentially play a role in assisting diagnostic procedures. Currently, the diagnosis of ADHD is solely based on behavioural measures that depend mainly on reports from parents and teachers, which are subjective and may be biased [94,95]. Furthermore, clinical descriptions of ADHD do not accurately predict the long term course and outcome in terms of persistence and development of associated comorbid symptoms. FMRI research has the potential to provide some 'hard' neurobiological indexes which, particularly in combination with genetic information (see five-year view below), could lead to better prediction of diagnostic status, course and outcome. Unfortunately, as we have seen, so far no consistent evidence has been produced at the single subject level of analysis, which would allow such use at the present time. Some studies do suggest that specific experimental paradigms might be sufficiently sensitive to differentiate between clinical groups [18] or individuals with or without a genetic vulnerability to ADHD [56], but this remains very uncertain at this time.

Although individual fMRI tests may not be sensitive and specific enough at the single subject level to be used for diagnostic purposes, summary measures based on more than one imaging paradigms which are combined together into a single clinical index may prove to be more useful. For example, multiple tests are included in the intelligence quotient because the results of any one test are insufficiently reliable. A fruitful approach for clinical use might therefore be to collect data from four or five fMRI paradigms that have been shown to discriminate between groups and use this multivariate data set to predict key clinical behavioural outcomes.

This would require further extensive research with healthy and clinical populations to establish normative patterns of brain activation characteristic of specific cognitive processes, as well as confidence intervals for the BOLD signal changes, so as to be able to compare an individual's responses and decide in which group they are likely to belong. Given the expense of fMRI research, this is not an easy task, and it would probably require more co-ordinated work with specific fMRI protocols which have been shown to elicit robustly activation in brain areas that have been implicated in ADHD pathophysiology. Fortunately, there seems to be some progress in this area [55,64]. A different but very promising approach for making status predictions, which is still at an experimental stage, would be to use pattern recognition analysis for the analysis of fMRI data, as Zhu and colleagues [21] did.

OVERVIEW AND EXPERT COMMENTARY

In Table 1 we present a summary of significant group differences in brain activation during tasks that tapped different aspects of executive functions. In the unshaded side of the table there are marked the regions in which the ADHD group showed lower activity compared to the control group in each study; in the shaded side of the table there are marked the regions where the ADHD group showed higher activity. From a simple visual overview of the table the following observations emerge:

- a. In tasks that examined brain activation during successful inhibitory control, there were large inconsistencies among studies in the direction of group differences.

Group differences were also spread across many different brain regions, but the frontal lobes were predominantly involved.

- b.** In analyses that examined inhibition errors, as well as in tasks that tapped attention processes, motor function and working memory, the ADHD group almost exclusively showed lower activity. In the attentional tasks this was mostly over temporal and parietal areas; in motor function tasks mostly over frontal areas.
- c.** Among the different brain regions, the most consistent findings as regards direction of activation were observed in the striatum. In all but one study [32] where significant group differences were observed, the ADHD group showed lower activity in the striatum. The only study where increased activation was observed had used a sample of adolescents of whom only half met full criteria for ADHD at the time of testing.
- d.** Finally, the group differences in the temporal and parietal cortices during attentional tasks (and to a lesser extent during inhibition control tasks) extend the sites of possible abnormalities in ADHD outside the fronto-striatal regions, calling for future fMRI research to study a greater range of cognitive and emotional processes.

The existence of abnormalities in the striatum in ADHD is corroborated by many different sources of evidence. Further to the functional abnormalities discussed above, activity in the striatum was negatively correlated with severity of hyperactivity/impulsivity symptoms, irrespective of the task performed and direction of group differences in other brain regions [58]. Moreover, a resting state study has found reduced blood volume in the striatum in ADHD [66]. The striatum also appears to be the primary site of action of MPH, the most widely used and effective drug treatment for ADHD [27,66,68]. This is not surprising since MPH mainly targets the dopamine transporter gene (DAT1) [96,97], which is primarily expressed in this region. In addition, genetic association studies suggest that genetic variation of the dopamine transporter gene is associated with ADHD and might also influence MPH response [8,9,98-100]. Structural differences in the striatum in children and adolescents have also been confirmed in a recent meta-analysis [70]; in a longitudinal study looking at the developmental trajectories of different brain regions, reduced volumes of the caudate nucleus during childhood were observed in the ADHD group, but in adolescence group volume differences tended to normalise [101]. The only structural study in adults with ADHD confirms this pattern, as it failed to find significant volume differences in the striatum between adult cases and controls [102]. They observed however a marginally significant trend for increased volume in the nucleus accumbens (NA) in the ADHD group. Given the involvement of the NA in reward processing [74,103] and its dysfunction in ADHD [18], this finding warrants further research.

An interesting finding emerging from the studies that examined the therapeutic effects of MPH is that its effects on striatal activation depended on the baseline levels of motor activity. In the study by Vaidya and colleagues [27] MPH increased activation in the ADHD group but decreased it in the control group, while in the study by Teicher and colleagues [66] it only increased activation in the most hyperactive children. The sensitivity of MPH to baseline activity levels raises concerns about the way symptoms are assessed in 'healthy' participants. It suggests that there might be a difference between complete absence of hyperactivity symptoms and sub-threshold hyperactivity, and calls for a more careful examination of this issue in future studies.

The existence of abnormalities in the frontal lobes in ADHD is supported by findings from fMRI studies that looked at inhibitory control, but also from the findings from resting state studies, and is further corroborated by evidence for structural abnormalities in youths with

ADHD [70] and in adults [102,104]. However, the numerous inconsistencies that were observed both in the direction of the differences as well as regarding the exact regions involved are puzzling. Some of the inconsistencies could be explained by the fact that the studies differed on many important aspects, such as sample characteristics, technical and methodological characteristics, as well as task details; it is worth examining some of these points in greater detail.

In general, samples differed in many respects (e.g. sex, age, comorbidity, medication status/history/length of wash-out period) between studies, the effects of which are each difficult to evaluate from the current range of studies. ADHD subtype and symptom severity differences are also likely to have impacted on the findings. In those studies that have reported subtype information, there were different mixes of inattentive and combined subtypes and almost no participants with the hyperactive/impulsive subtype. It is also likely that among participants with combined type ADHD or hyperkinetic disorder, some were excluded due to excessive movement. For example, in the study by Durston and colleagues [57] as many as 50% of the ADHD group were excluded for this reason. Clearly, this raises concerns about selection biases, whereby the most severe cases are excluded, and about the generalisability of findings to clinic populations. Event-related and block design studies have tended to use exclusively or predominantly youths with ADHD-combined type [27,35,39,42,50,56,62], although in some of them the ratios were more balanced between the combined and the inattentive subtypes [17,26,57,58]. It is interesting that in the studies by Durston and colleagues [56,57], which produced such markedly different results for group differences in brain activation, subtype ratios and age ranges were among the few study differences. In the resting state studies by Cao, Zang, Tian and colleagues [19,89,90], the clinical samples were composed predominantly of youths of the inattentive subtype. The effects of subtype type on brain activation are an issue that has yet to be addressed in fMRI research.

There were also many technical and methodological differences among the studies. There were differences in the strength of the magnet (1.5 or 3 Tesla, which affects the amplitude of signal changes that can be detected), in the imaging protocols, the methods of analysis, as well as in the statistical thresholds that were used to detect significance. Variations in all of these aspects can alter findings from study to study.

A further and perhaps the most important methodological concern regards the small sample sizes that have been used, although more recent studies have tended to increase the number of participants. Small sample sizes mean reduced power to detect significant differences, which constitutes findings from single studies unreliable [51]. Moreover, there is a lack of sufficient evidence on the test-retest reliability of the fMRI data; information about the reliability of measurements is necessary when considering the required sample sizes. This makes replications particularly important.

Finally, even subtle differences in task details or in baseline conditions [26,27] may produce quite different results, as we have seen. For example, studies that used different tasks with the same samples found decreases in activation in opposite sides of the frontal lobes, depending on the particular inhibitory task they used [35,39,62].

However, such sampling or technical and methodological differences could not possibly fully explain the inconsistencies between studies. The same differences also held for studies that examined attentional processes, yet the results were far more consistent, at least as regards their direction (see table 1). Another reason that could have contributed to the abnormalities observed during the inhibitory control tasks relates to the physiology of the prefrontal cortex, and it might be worth examining this argument in some detail.

Schulz and colleagues interpreted the frontal hyperactivation in their ADHD group [32,40,61] as a reflection of the increased effort the participants had to make to meet task demands, given that overall they seemed to find the task more difficult, as confirmed by their worse performance. Findings from these studies associated impaired performance and severity of inattention symptoms with increased activation at the frontal cortex [32,40]. However, other studies in which the ADHD group showed hypoactivation found that more severe levels of hyperactive and impulsive symptoms were associated with hypoactivation in the VLPFC [39] and the striatum [18,58]; and that improved performance was associated with increased activity in the VLPFC, the mesial parietal lobes, the temporal lobes [39] and the left parietal lobe [67].

Studies that have examined the function of the prefrontal cortex in the context of cognitive tasks such as working memory have found an inverted 'U' relationship between increases in task difficulty and BOLD signal change in frontal regions. This means that as task difficulty increases, frontal activation may increase up to a point, and after reaching a peak (corresponding to the limits of working memory capacity), it starts decreasing [105]. Task difficulty is not though an objective feature embedded in the task. Under a capacity model of cortical function, a demand on capacity-limited processing resources is not only made by task-related demands but also by pathological processes, which are competing for the same resources [29,106]. Moreover, prefrontal function has also been shown to be modulated by dopamine availability, which is regulated by genetic factors [45]. Therefore task difficulty would be a function of objective task features, symptom severity but also system characteristics (e.g. DA related gene variants), thus both increases and decreases in prefrontal cortical activity would be expected depending on the dynamics of the factors mentioned above (see [107] for an example from research in schizophrenia). Moreover, inattentiveness and hyperactivity/impulsivity might impact differently on this system (with the limited evidence discussed above showing opposite correlations with prefrontal activity). The seemingly contradictory findings should therefore not surprise us, and here we have suggested a model that could possibly accommodate them.

FIVE-YEAR VIEW

Further research must address the issues raised above. As a recent review suggests [108], there is converging evidence from multiple sources that supports a DA deficit theory for ADHD. DA related genetic polymorphisms affect prefrontal function and cognitive performance, and have been associated with increased risk for ADHD. Therefore, their impact on brain function in the context of ADHD should be examined in more detail. An ideal tool for this job would be imaging genetics [109], which we believe will play an important role in fMRI research in ADHD in the immediate future, as it has done so far in other areas such as schizophrenia [110]. Research into the neurobiology of ADHD is likely to benefit from the use of molecular genetics findings to inform research design. Imaging genetics can offer consistent evidence to illuminate the pathways that link individual variations in genes, and consequently in protein and cell function, to the clinical expression of cognitive, emotional and behavioural symptoms and signs that are characteristic of this disorder. Moreover, the identification of the mediating neural mechanisms can help back molecular research, by suggesting further genetic variants that are known to impact on these systems. The examination of the effects of genetic variants is likely to be best approached by considering groups of interacting and co-acting polymorphisms in, for example, genes that regulate dopamine and related neurotransmitter systems. Whether fMRI patterns will provide better 'brain phenotypes' for gene finding studies remains an area of uncertainty, but there is recent evidence that some genes show much higher penetrance at this level [111].

Technical advancements both in magnetic resonance imaging technology as well as in methods of analysis are going to expand the range of phenomena that can be studied and the kind of questions that can be addressed. For example, arterial spin labelling [84] provides a non-invasive, quantitative measurement of brain function, and the use of pattern recognition analysis techniques in data analysis may open up new ways for the use of fMRI to inform diagnostic procedures. Finally, etiological hypotheses in ADHD have moved beyond executive dysfunction, and we can predict that fMRI research will follow suit. New theories pose important questions regarding the functioning of reward processing mechanisms, motivation and arousal regulation in ADHD, and these are issues that will be increasingly addressed by research in the immediate future.

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Box 1**The BOLD signal**

FMRI studies commonly use blood oxygen level dependent (BOLD) signal changes to visualise brain activity. BOLD fMRI provides an indirect measure of neural activity, the detection of which depends on the comparison of BOLD signals between different experimental conditions. It does not allow the quantitative measurement of cerebral blood flow or volume. Although there are recent fMRI techniques that can measure blood flow quantitatively, such as arterial spin labelling (ASL) [Petersen ET, Zimine I, Ho YC, Golay X. Non-invasive measurement of perfusion: a critical review of arterial spin labelling techniques. *Br. J. Radiol.*, 79(944), 688-701 (2006)], they have yet to appear in published reports on ADHD.

The BOLD signal is generated by the ratio of oxygenated to deoxygenated haemoglobin (dHb). Haemoglobin molecules in the red blood cells carry oxygen (O_2) to the brain and the consumption of O_2 produces dHb, which has paramagnetic properties. Increases in neural activity result in an increase in O_2 consumption to meet metabolic demands (and thus an increase of dHb), but also in a disproportional increase in cerebral blood flow and glucose metabolism. As a consequence of the disproportional influx of oxygenated haemoglobin with the increase in blood flow, the ratio of oxygenated haemoglobin to dHb also increases. Changes in this ratio are correlated with changes in the magnetic resonance signal allowing the study of brain function in vivo [Amaro E, Jr., Barker GJ. Study design in fMRI: basic principles. *Brain Cogn.*, 60(3), 220-232 (2006); Logothetis NK. The neural basis of the blood-oxygen-level-dependent functional magnetic resonance imaging signal. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.*, 357(1424), 1003-1037 (2002)]. For short stimulus presentations, BOLD signal changes are proportional to local neural activity, while for prolonged stimulus presentation periods the signal reaches a plateau, before it drops after cessation of stimulus presentation [Amaro E, Jr., Barker GJ. Study design in fMRI: basic principles. *Brain Cogn.*, 60(3), 220-232 (2006); Logothetis NK. The neural basis of the blood-oxygen-level-dependent functional magnetic resonance imaging signal. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.*, 357(1424), 1003-1037 (2002)].

KEY ISSUES

- ADHD is the most common psychiatric disorder in childhood and is highly heritable.
- It is associated with impairment in many (executive) cognitive functions and has been associated with dysfunction in reward processing mechanisms and the self-regulation of arousal.
- FMRI is a safe and highly promising brain imaging tool, which enables us to understand the neurobiological mechanisms that underlie ADHD.
- Individuals with ADHD show a dysfunction in the frontal lobes during tasks that tap inhibitory control, although there are inconsistencies regarding the exact nature of the problem.
- A dysfunction in temporal and parietal areas also plays a role, mostly during tasks that examine attentional processes.
- The most consistent evidence shows that patients with ADHD demonstrate reduced activation in the striatum.
- Studies that examined the therapeutic effects of methylphenidate show that its effects on striatal activation depend on baseline levels of motor activity.

Figure 1.

Schematic representation of block and event-related designs. **Diagram A** (top) represents part of a block design experiment; the experimental and control conditions are presented interchangeably. In the experimental condition, target and control events are interspersed; the recorded BOLD signal response represents an aggregate of neural activity to both kinds of stimuli. In the control condition only control events are presented. The solid line represents the recorded BOLD fMRI signal, while the dotted line stands for our model of the haemodynamic response function against which the fMRI BOLD signal is evaluated. **Diagram B** (bottom) represents an event-related design, where the BOLD response to each event (solid line) is recorded and analysed separately. Different models (dotted line) allow us to distinguish between different event types.

Statistically significant differences in brain activation between ADHD and healthy comparison groups during executive function tasks.

Table 1

Cognitive function/task			Group differences in brain activation per region																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																															
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Note: The table presents group differences in the most commonly reported brain regions. Rough anatomical subdivisions have been used; for more precise information about the exact location of group differences please refer to individual papers.

Abbreviations: L=left, R=right, BL=bilateral, X=not specified, ER=event-related, BD=block design, SC=stimulus-controlled, RC=response-controlled, alertn.=alertness, Reor.=reorienting, ASA=auditory selective attention, DA=divided attention, VLPFC=ventrolateral prefrontal cortex, DLPFC=dorsolateral prefrontal cortex, dACC=dorsal anterior cingulate cortex, mPFC=mesial prefrontal cortex, OFC=orbitofrontal cortex, PCC=posterior cingulate cortex, STR=striatum, IPL/SPL=inferior/superior parietal lobe, mPC=mesial parietal cortex, STG/MTG/ITG=superior/middle/inferior temporal gyrus, CRB=cerebellum, OC=occipital cortex.

^aOnly the studies that used event-related designs analysed successful inhibition trials separately.