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ORIGINAL ARTICLE

Identifying a consistent pattern of neural function in attention deficit hyperactivity disorder: a meta-analysis

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Background. The neurobiological underpinnings of attention deficit hyperactivity disorder (ADHD) are inconclusive. Activation abnormalities across brain regions in ADHD compared with healthy controls highlighted in task-based functional magnetic resonance imaging (fMRI) studies are heterogeneous. To identify a consistent pattern of neural dysfunction in ADHD, a meta-analysis of fMRI studies using Go/no-go, Stop and N-back tasks was undertaken.

Method. Several databases were searched using the key words: 'ADHD and fMRI' and 'ADHD and fMRI task'. In all, 20 studies met inclusion criteria comprising 334 patients with ADHD and 372 healthy controls and were split into N-back, Stop task and Go/no-go case–control groups. Using Signed Differential Mapping each batch was meta-analysed individually and meta-regression analyses were used to examine the effects of exposure to methylphenidate (MPH), length of MPH wash-out period, ADHD subtype, age and intelligence quotient (IQ) differences upon neural dysfunction in ADHD.

Results. Across all tasks less activity in frontal lobe regions compared with controls was detected. Less exposure to treatment and lengthier wash-out times resulted in less left medial frontal cortex activation in N-back and Go/no-go studies. Higher percentage of combined-type ADHD resulted in less superior and inferior frontal gyrus activation. Different IQ scores between groups were linked to reduced right caudate activity in ADHD.

Conclusions. Consistent frontal deficits imply homogeneous cognitive strategies involved in ADHD behavioural control. Our findings suggest a link between fMRI results and the potentially normalizing effect of treatment and signify a need for segregated examination and contrast of differences in sample characteristics in future studies.

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Key words: Attention deficit hyperactivity disorder, functional magnetic resonance imaging, meta-analysis, tasks.

Introduction

Attention deficit hyperactivity disorder (ADHD) is characterized by the onset of developmentally inappropriate levels of impairing inattention, hyperactivity and impulsivity before the age of 7 years. ADHD is one of the most common mental disorders with a worldwide prevalence estimate of 5.29% and a heritability estimate of about 76% (Faraone *et al.* 2003). ADHD is no longer considered a disorder exclusive to childhood: approximately 15% of adults with a previous diagnosis of childhood ADHD meet full criteria for ADHD, approximately 65% show partial remission and only approximately 20% show complete remission in adulthood (Faraone *et al.* 2006).

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Accurately diagnosing adults with ADHD is difficult, as the diagnostic criteria for ADHD are founded upon research conducted upon individuals aged between 4 and 17 years (Frodl, 2010). The clinical presentation of ADHD changes with increasing age (Faraone *et al.* 2006); the hyperactive and impulsive symptoms of childhood ADHD become less pronounced, while inattentive symptoms persist (Biederman *et al.* 2000). Emotional dysregulation and disorganization characteristically accompany persistent inattentive symptoms in adult ADHD (Greydanus *et al.* 2007). ADHD in adulthood is socially and occupationally debilitating and is significantly associated with co-morbid depression, anxiety and substance abuse (Frodl, 2010).

Neuroimaging may provide some insights into the neurobiological underpinnings of ADHD. Inattention, impulsivity, impaired executive functioning and sensorimotor timing can be directly linked to functional changes within certain brain regions using functional magnetic resonance imaging (fMRI). The majority of

ADHD fMRI studies in both adults and children have utilized cognitive activation paradigms that target the neural circuits sub-serving the skills impaired in ADHD (Martinussen *et al.* 2005). Prevalent paradigms include the N-back, Go/no-go and Stop task.

The N-back task measures the neural components underlying working memory performance and has been associated with fronto-parietal region activation (Valera *et al.* 2005). Performance accuracy necessitates the inhibition of responses to irrelevant task stimuli while monitoring, manipulating and updating remembered information (Owen *et al.* 2005; Kobel *et al.* 2009). Previous N-back studies found that compared with controls, ADHD patients typically hypo-activate bilateral middle frontal, cerebellar, occipital and parietal areas (Valera *et al.* 2005; Kobel *et al.* 2009; Bayerl *et al.* 2010).

Methylphenidate (MPH) has been found to mediate dysfunctional neural activation between children with ADHD and controls when performing the Stop task which requires response inhibition (Rubia *et al.* 2011*b*). However,when children with ADHD stopped taking medication they underactivated the posterior and right anterior cingulate, precuneus and orbitofrontal cortex compared with controls (Rubia *et al.* 1999, 2009*c*, 2010, 2011*b*). A Stop task study of an adolescent sample of ADHD participants found that they exhibited less activation compared with controls across prefrontal regions such as the dorsolateral prefrontal cortex (DLPFC), superior temporal gyrus and bilateral ventrolateral prefrontal cortex, all of which are necessary for higher-order decision making and the timing of motor responses (Passarotti *et al.* 2010).

The Go/no-go task is a measure of selective motor response inhibition and has been linked to activation within the pre-supplementary motor area, fronto-temporal, prefrontal and parietal circuits (Simmonds *et al.* 2008). Neurofunctional deficits amongst ADHD participants within prefrontal, fronto-striatal and parietal regions (Mulligan *et al.* 2011) have been consistently shown throughout the literature (Dickstein *et al.* 2006). For example, compared with controls under the 'no-go' response inhibition condition, ADHD adults typically display hypo-activation of the bilateral superior frontal gyri, left superior parietal lobules and left anterior cingulate (Durston, 2006; Schneider *et al.* 2010). Similarly ADHD children when required to inhibit a response have been shown to display less activity compared with controls within the inferior middle, superior and medial frontal gyri (Booth *et al.* 2005; Smith, 2006) as well as within the caudate nucleus and globus pallidus (Tamm *et al.* 2004). However, with incoherent instances of hyperactivation throughout ADHD sample groups within parietal (Dillo *et al.* 2010) and fronto-striatal regions such as the putamen and inferior frontal gyrus (Dibbets *et al.* 2009; Kooistra *et al.* 2010; Schneider *et al.* 2010) it is difficult to attribute functional deficits to one specific area.

The results generated from each of the tasks are varied; hence several aims for the present meta-analysis were formulated:

(1) To investigate whether and in which brain regions patients with ADHD exhibit less activity compared with controls across tasks and whether this differs between children and adults.
(2) To examine the influence of confounds such as previous treatment with MPH, length of wash-out period from MPH, ADHD subtypes, gender distribution, age and unmatched intelligence quotient (IQ) scores upon neurofunctional differences between ADHD participants and controls.

The ultimate goal of this meta-analysis was to identify more consistent patterns of ADHD dysfunction and elucidate the mechanisms by which treatments for ADHD work through increased understanding of the neural circuitry of attention, cognition and reward.

Method

Literature search

An extensive search of databases, including Pubmed, Science Direct, Web of Knowledge and Scopus were searched using the following key words: 'ADHD and fMRI' and 'ADHD and fMRI task'. Studies included were published no later than January 2012. Selected articles, as criteria for inclusion, had to: (1) conduct fMRI analysis using functional tasks; (2) compare differences in brain activation between ADHD participants and healthy controls; (3) report whole brain correction methods such as familywise error correction, false discovery rate or cluster enhanced thresholding; and (4) report an original study. The search was confined to English language articles.

Exclusion criteria for the final meta-analysis were: (1) region of interest (ROI) studies (as these violate the assumption, under the null hypothesis, that the likelihood of locating activated foci is equal at every voxel); (2) studies of ADHD participants with co-morbid psychiatric disorders; (3) studies containing duplicated datasets; (4) literature reviews; (5) single case studies; and (6) studies that only used screening instruments to confirm the diagnosis of ADHD.

Meta-analysis of studies

Three batches of studies involving the different functional tasks, N-back, Stop task and Go/no-go emerged from the literature search and each batch was meta-analysed individually as the tasks differed in structure

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and the cognitive strategies they prompted participants to use. Peak coordinates of activation could then be attributed to the conditions of one form of task.

The meta-analytical differences in blood oxygen level-dependent (BOLD) activity between participant groups were calculated using mean and threshold probability procedures with Signed Differential Mapping (SDM; http://www.sdmproject.com). This software uses restricted maximum likelihood estimation of the variance with the reported peak coordinates to recreate maps of the positive and negative BOLD differences between patients and controls rather than just assessing the probability of likelihood of a peak. This unique feature makes SDM an optimal method for comparing patients with controls without biasing the results toward those brain regions with more inter-study heterogeneity.

SDM converts fMRI coordinates to Talairach space with cluster peaks being represented on an SDM or MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron/) brain map highlighting areas of the brain where BOLD activity reaches significant value, with positive and negative changes being represented by different colours. Peaks that are not statistically significant at the whole-brain level are excluded from these maps. This is carried out in order to ensure that the same statistical threshold throughout the brain is used within each study. Therefore, biases towards liberally thresholded brain regions are avoided, as it is not uncommon in neuroimaging studies that the statistical threshold for some ROIs is more liberal than for the rest of the brain. Next a standard Talairach map of the differences in activity is recreated separately for each study by means of a Gaussian kernel that assigns higher values to voxels closer to peaks. This includes: (1) limiting voxel values to a maximum to avoid bias to studies reporting various values in close proximity; and (2) reconstructing both increases and decreases in activity in the same map. Mean analysis, which calculates the mean of each voxel, was carried out in our meta-analysis, with studies containing a larger sample size having more weight.

Jack-knife analysis was also carried out on the included studies to ensure that one study did not significantly affect our results and that the Talairach coordinates obtained were highly replicable throughout all of the studies. Moreover, descriptive analyses of quartiles were used to find the actual proportion of studies reporting results in a particular brain region. Statistical significance was determined using standard randomization tests, thus creating null distributions from which p values could be obtained directly. We focused upon results with $p<0.005$ for significance for between-group differences and $p<0.001$ for the meta-regression analysis.

Meta-regression analyses were carried out to explore whether exposure to MPH, length of MPH wash-out period, ADHD subtype, age, gender and IQ differences between groups were predictors of neurofunctional differences between ADHD participants and controls.

Results

Included studies and sample characteristics

An exhaustive database search conducted resulted in over 701 publications up to a publication cut-off date of 30 January 2012. The basis for which 668 studies had to be excluded can be seen in online Supplementary Fig. S1. This resulted in 20 high-quality datasets being selected for inclusion in the meta-analysis. Combined, the studies included 334 ADHD participants: N-back (111 participants; Valera *et al.* 2005; Kobel *et al.* 2009; Bayerl *et al.* 2010; Valera & Brown, 2010); Stop task (74 participants; Rubia *et al.* 1999, 2000, 2010, 2011*a*; Cubillo *et al.* 2010; Passarotti *et al.* 2010); Go/no-go (149 participants; Tamm *et al.* 2004; Booth *et al.* 2005; Durston *et al.* 2006; Smith, 2006; Suskauer *et al.* 2008; Dibbets *et al.* 2009; Kooistra *et al.* 2010; Schneider *et al.* 2010; Dillo *et al.* 2010; Mulligan *et al.* 2011) and 374 controls (N-back: 113 controls, Stop task: 102 controls, Go/no-go: 159 controls).

The results from the SDM analysis were converted into brain maps and visualised using MRIcron software (http://www.mccauslandcenter.sc.edu/mricro/mricron/) which were then cross-compared with a Talairach map to optimally localise the brain regions most probably involved. Coordinates for the SDM meta-analysis and sample characteristics for the meta-regression analyses were obtained from all of the studies detailed in online Supplementary Tables A, B and C. Jack-knife sensitivity analysis results including the descriptive analysis of quartiles for each study may be found within the online Supplementary information.

N-back task results

Between-group differences

Patients with ADHD displayed less activity than control participants who underwent the N-back task in the bilateral superior frontal gyri and left medial frontal gyrus when we examined the mean diagnostic differences between the two groups (Table 1, section 1.1; Fig. 1).

N-back task meta-regression results

Gender. Using linear regression we explored whether gender could be linked to activation variance throughout the sample groups. Higher percentage of females

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Table 1. *Overall group differences*

Peak voxel in region	Talairach coordinates: x, y, z	SDM value	Uncorrected *p* value	Voxel number	Breakdown (number of voxels)
Mean difference in activation between groups during the N-back task					
1.1 Controls>ADHD					
Right superior frontal gyrus	34, 54, 26	−1.444	0.00154	119	R SFG (82) R MFG (37)
Left superior frontal gyrus	−26, 44, 22	−1.432	0.00168	23	L SFG (15) L MFG (8)
Left medial frontal gyrus	−14, 40, 14	−1.321	0.00168	24	L medial frontal gyrus (12) L ACC (12)
Mean difference in activation between ADHD children *v.* control children during the Stop task					
2.1 Controls>ADHD					
Right inferior frontal gyrus	42, 20, −2	−2.481	0.00001	293	R IFG (155) R sub-lobar insula (123) R MFG (15)
Left inferior frontal gyrus	−50, 16, 10	−1.578	0.00019	113	L IFG (86) L PCG (27)
Right medial frontal gyrus	4, 44, 20	−1.541	0.00037	25	R MFG (21) L MFG (4)
Right superior frontal gyrus	22, 56, −8	−1.510	0.00102	46	R SFG (36) R medial frontal gyrus (6) R MFG (4)
Right middle frontal gyrus	46, 22, 30	−1.478	0.00078	10	R MFG (10)
Right superior frontal gyrus	18, 30, 50	−1.404	0.00193	68	R SFG (63) R medial frontal gyrus (5)
Mean difference in activation between ADHD and controls during Go/no-go tasks					
3.1 Controls>ADHD					
Left medial frontal gyrus	−10, 4, 54	−1.787	0.00001	187	L medial frontal gyrus (128) L ACC (35) L SFG (19) R medial frontal gyrus (5)
Right caudate	10, 12, 4	−1.451	0.00035	106	R caudate head (106)
3.2 Control adults>ADHD adults					
Left medial frontal gyrus	14, −12, 52	−1.769	0.00001	341	L MFG (215) L ACC (65) L MFG (26) L sub-gyral (21) L paracentral lobule (10) L SFG (4)
Right inferior parietal lobule	46, −50, 38	−1.579	0.00025	41	R IFG(38) R supramarginal gyrus (1) R angular gyrus (2)
Mean diagnostic differences in activation between ADHD children and control children					
3.3 ADHD children>control children					
Right middle frontal gyrus	2, 58, 0	1.061	0.00014	88	R MFG (2) L MFG (54) L SFG (26) L MFG (3) L ACC (3)
3.4 Control children>ADHD children					
Right superior frontal gyrus	24, 48, 20	−1.422	0.00001	50	R SFG (28) R MFG (22)

SDM, Signed Differential Mapping; ADHD, attention deficit hyperactivity disorder; R, right; SFG, superior frontal gyrus; MFG, middle frontal gyrus; L, left; ACC, anterior cingulate cortex; IFG, inferior frontal gyrus; PCG, pre-central gyrus.

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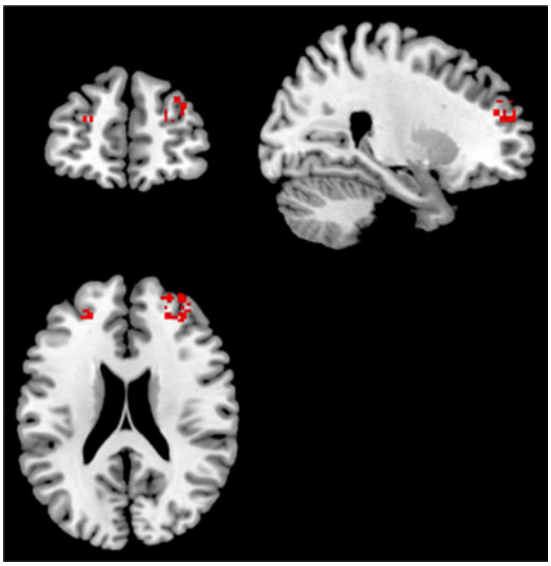

Fig. 1. Mean diagnostic differences between attention deficit hyperactivity disorder (ADHD) and healthy control participants within the batch of N-back studies. ADHD participants displayed less activity than control participants in the right superior frontal gyrus [Talairach coordinates: x=34, y=54, z=26; Signed Differential Mapping (SDM) value=−1.44; $p \leqslant 0.000154$; 119 voxels] and left superior frontal gyrus (Talairach coordinates: x=−26, y=44, z=22; SDM value=−1.43; $p \leqslant 0.00168$; 23 voxels). The left medial frontal gyrus (Talairach coordinates: x=−14, y=40, z=14; SDM value=−1.32; $p \leqslant 0.00168$; 24 voxels) also activated less in ADHD participants compared with controls (not shown here).

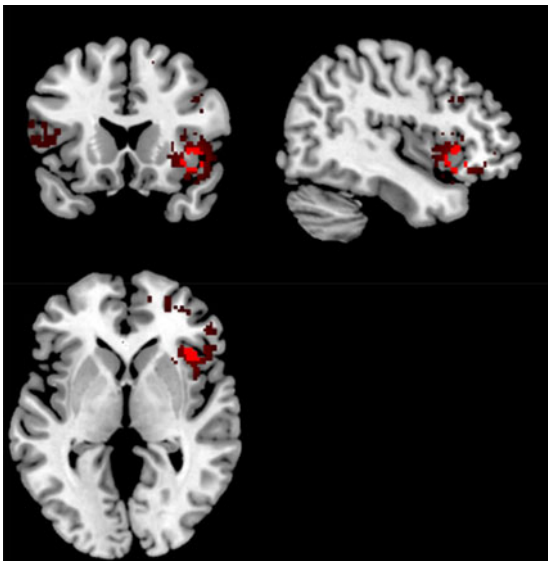

Fig. 2. Mean diagnostic differences between attention deficit hyperactivity disorder (ADHD) and healthy control participants within the batch of Stop task studies. This examination revealed that control children activated the right inferior frontal gyrus [Talairach coordinates: x=42, y=20, z=−2; Signed Differential Mapping (SDM) value=−2.38; $p \leqslant 0.00001$; 293 voxels], left inferior frontal gyrus (Talairach coordinates: x=−50, y=16, z=10; SDM value=−1.57; $p \leqslant 0.00019$; 113 voxels), right medial frontal gyrus (Talairach coordinates: x=4, y=44, z=20; SDM value =−1.54; $p \leqslant 0.00037$; 25 voxels) and right middle frontal gyrus (Talairach coordinates: x=46, y=22, z=30; SDM value =−1.47; $p \leqslant 0.00078$; 10 voxels) more than ADHD children.

in studies was associated with greater activation differences in the left cerebellum ($p \leqslant 0.001$) and left inferior occipital gyrus ($p \leqslant 0.001$), with higher activation in ADHD compared with controls (online Supplementary Table S1, section 1.2).

Treatment history. Linear-regression analysis revealed that the percentage of those with less exposure to treatment were linked to less activity in ADHD compared with controls in the left middle frontal gyrus ($p \leqslant 0.001$) and bilateral superior frontal gyri ($p \leqslant 0.001$) (online Supplementary Table S1, section 1.4).

ADHD subtype. ADHD type varied across studies, so a linear regression of variance between non-combined-type ADHD and combined-type ADHD participants was carried out. The percentage of combined-type ADHD correlated with more positive difference in ADHD than controls within the right cerebellum ($p \leqslant 0.001$) (online Supplementary Table S1, section 1.5). The percentage of combined-type ADHD correlated with more negative difference within the left declive ($p \leqslant 0.001$) and left inferior occipital gyrus ($p \leqslant 0.001$) in ADHD compared with controls (online Supplementary Table S1, section 1.6).

All but one of the studies included adults; therefore distinguishing between child and adult studies did not need to be undertaken. Distinguishing the effect of IQ differences upon this sample was not necessary as all but one of the studies were matched for IQ.

Stop task results

Between-group differences

With the exception of one adult study, the remaining five studies examined children exclusively. Therefore we examined the mean diagnostic differences between control children and ADHD children within this batch of Stop task studies. This examination revealed that ADHD children activated the bilateral inferior frontal gyri, right superior frontal gyrus and right middle frontal gyri significantly less than control children (Fig. 2; Table 1, section 2.1).

Stop task meta-regression results

Age. Linear regression revealed that older age in childhood was linked to more positive differences in ADHD

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compared with controls in the right inferior frontal gyrus ($p \leqslant 0.00001$) (online Supplementary Table S2, section 2.2).

Treatment history. A lower percentage of treatment in ADHD was linked to more difference within the right superior frontal gyrus ($p \leqslant 0.0002$) compared with controls and those with ADHD who had more previous treatment (online Supplementary Table S2, section 2.3).

Linear regression revealed that a higher percentage of treatment in ADHD was linked to more activation within the left cerebellum ($p \leqslant 0.0001$) compared with controls and patients with ADHD with a lower percentage of treatment (online Supplementary Table S2, section 2.4).

ADHD subtype. Differences in ADHD type warranted investigation using linear regression, as the ADHD population was not exclusively combined-type. Lower percentage of combined-type ADHD was linked to decreased activation within the right insula ($p \leqslant 0.00001$), right middle frontal gyrus ($p \leqslant 0.00001$), right medial frontal gyrus ($p \leqslant 0.00014$) and left thalamus ($p \leqslant 0.000015$) compared with controls (online Supplementary Table S2, section 2.5).

Higher percentage of combined-type ADHD was then associated with less activation in the right superior frontal gyrus ($p \leqslant 0.00001$) and right inferior frontal gyrus ($p \leqslant 0.00003$) compared with controls (online Supplementary Table S2, section 2.6).

IQ differences. When the effect of the differences in overall IQ scores between both groups was examined, studies in which IQ scores were less matched, the right superior parietal lobule ($p \leqslant 0.00011$) and the bilateral medial frontal gyri ($p \leqslant 0.00025$) were less activated for ADHD participants than controls (online Supplementary Table S2, section 2.7).

A regression with percentage of gender was not necessary to be carried out, as the majority of participants were male.

Go/no-go task results

Between-group results

Within the Go/no-go task studies, ADHD participants had significantly less mean activation in the left medial frontal gyrus and right caudate than controls (Table 1, section 3.1; Fig. 3).

An examination of the mean diagnostic differences between ADHD adults and control adults revealed that control adults activated the left medial frontal gyrus and the right inferior parietal lobule more so than ADHD adults (Table 1, section 3.2). By contrast, the mean diagnostic difference between ADHD children and control children was that more activation was found in ADHD children within the right middle frontal gyrus (Table 1, section 3.3). Control children activated the right superior frontal gyrus more than ADHD children (Table 1, section 3.4).

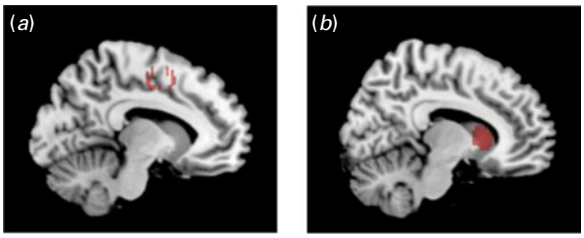

Fig. 3. Mean diagnostic differences between attention deficit hyperactivity disorder (ADHD) and healthy control participants within the batch of Go/no-go task studies. This examination revealed that ADHD participants activated the (*a*) left medial frontal gyrus [Talairach coordinates: x = −10, y = 4, z = 54; Signed Differential Mapping (SDM) value = −1.787; $p \leqslant 0.001$; 187 voxels] and (*b*) right caudate (Talairach coordinates: x = 10, y = 12, z = 4; SDM value = −1.451; $p \leqslant 0.001$; 106 voxels) to a lesser extent than control participants.

Go/no-go task meta-regression results

Age in adulthood. A linear regression to uncover activation associated with adulthood showed that increased age in adulthood coincided with higher activation within the bilateral lingual gyri and left fusiform gyrus (online Supplementary Table S3, section 3.5) relative to younger ADHD adults and controls. However, within the right thalamus, older ADHD adults had lower activation relative to younger ADHD participants and controls (online Supplementary Table S3, section 3.6).

Age in childhood. Also, with increased age in children more positive differences within the left inferior temporal gyrus and left inferior frontal gyrus were more apparent than for those of younger children with ADHD and controls (online Supplementary Table S3, section 3.7).

Treatment history. Linear regression revealed that a higher percentage of treated adults in studies were linked to fewer activity differences in the right caudate and right superior frontal gyrus in ADHD compared with controls (online Supplementary Table S3, section 3.8). However a smaller percentage of treatment in adulthood samples was then linked to less activity in the left fusiform gyrus in ADHD compared with controls (online Supplementary Table S3, section 3.9).

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Wash-out period. Within this sample of studies the length of wash-out periods from medication varied. Longer wash-out periods meant more activation differences compared with controls in the right precuneus for ADHD participants. Shorter wash-out periods for patients with ADHD meant fewer activation differences compared with controls in the left medial frontal gyrus (online Supplementary Table S3, sections 3.10, 3.11).

ADHD subtype. Studies with a high percentage of combined-type ADHD were linked to less activation of the right caudate compared with controls (online Supplementary Table S3, section 3.12). A high percentage of combined-type ADHD was linked to more activation of the left fusiform and right lingual gyri (online Supplementary Table S3, section 3.13).

IQ differences. Studies with lower mean IQ scores in the ADHD groups compared with control groups showed higher activity within the left fusiform gyrus and right lingual gyrus for ADHD participants compared with controls (online Supplementary Table S3, section 3.14). The left superior frontal gyrus and right caudate showed higher activation for controls than for ADHD participants with lower mean IQ scores (online Supplementary Table S3, section 3.15). When studies did not have the same mean IQ score in both ADHD and control groups, there was more activity within the right thalamus for ADHD participants relative to controls (Supplementary Table S3, section 3.16). These studies also showed reduced activation in the right inferior parietal lobule and left precuneus in ADHD groups compared with controls when IQ scores were not equally matched (online Supplementary Table S3, section 3.17).

Discussion

This meta-analysis demonstrated important consistent findings within ADHD research, but also high variability between studies due to different sample characteristics with respect to treatment history, wash-out time, IQ differences and ADHD subtypes.

Across all meta-analysed tasks, ADHD participants showed significantly less frontal lobe activity compared with controls. This finding might be unsurprising as all three tasks necessitate the use of skills impaired in ADHD which utilize frontal regions, such as the middle frontal and inferior frontal gyri in working memory and inhibitory control (Valera *et al.* 2005; Fassbender *et al.* 2011); the medial frontal gyrus in self-regulation (Simmonds *et al.* 2008; Rubia *et al.* 2011*a*); and the superior frontal gyri and prefrontal cortices in motor planning, alerting behaviour and impulsivity control (Pliszka *et al.* 2006; Rubia *et al.* 2009*b*).

Effect of treatment

Treatment effects are an important consideration for future work as treatment naivety and lengthier wash-out periods from MPH accounted for an extensive level of significant variability between groups and highlighted the potentially normalizing effect of MPH within this meta-analysis.

The robust decreases within the left medial frontal cortex, which were more pronounced in participants with ADHD with less treatment history and exposure to treatment at the time of investigation in N-back and Go/no-go studies, might indicate an acute and long-term effect of treatment with MPH. This finding was also highly replicable across studies and interestingly studies that imposed a longer wash-out period – for more than 2 days and longer – showed greater differences in this region. This indicates that acute medication has a significant effect upon medial frontal gyrus activity and that there may be an effect stemming from MPH lasting longer than 48 h. As the half life of MPH is estimated to be 6 h (Volkow & Swanson, 2003), this finding is interesting as it supports the notion that MPH may act longer upon dopamine transporters in the nervous system and upon functional changes than expected (Volkow *et al.* 2002).

Also, the left medial frontal gyrus is an area involved in successful error detection (Garavan *et al.* 2002) which is impaired in ADHD (Cubillo *et al.* 2011). Our results suggests that MPH may moderate poor error detection, as those with a history of previous treatment displayed normalized frontal activation akin to controls (Owen *et al.* 2005).

The potential normalization of medial frontal cortex dysregulation in ADHD through treatment is pertinent to ADHD research because this region is involved in facilitating the interplay between cognition and emotions (Posner *et al.* 2011). Hypo-activity in this area has been linked to a predilection for violent behaviour and impaired impulse control (Davidson *et al.* 2000). Emotional dysregulation and disorganization characteristically accompany persistent inattentive symptoms in adult ADHD (Greydanus *et al.* 2007). Therefore, normalization of medial frontal cortex activation may induce a learning effect upon cognitive and emotional regulation over time during successful treatment.

Within Go/no-go studies there was less right caudate activation, a region involved in the regulation of motivation and emotion (Proal *et al.* 2011) which has been found to be smaller in volume amongst ADHD children and adolescents alike (Frodl & Skokauskas,

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2012). Linear regression showed that this was more likely to be found in studies with a lower number of pre-treated subjects and in studies with different IQ scores between control and ADHD participants. Reduced right caudate and left medial frontal activation is in line with findings from Simon Task fMRI studies that examined inhibitory control in ADHD patients with less exposure to treatment (Rubia *et al.* 2011*b*; Cubillo *et al.* 2011; Sebastian *et al.* 2012).

Moreover, changes in the right superior frontal gyrus were found in the Stop task and N-back studies, particularly amongst those with ADHD who were treatment naive, suggesting an important role for this region in ADHD. The superior frontal gyrus is involved in optimum alerting behaviour and motor planning in which ADHD participants have been found to activate more posterior regions such as the occipital gyri and cerebellum with lengthier response times than controls (Cao *et al.* 2008; Vloet *et al.* 2010).

Previous studies found that acute and chronic treatment with MPH was insufficient in normalizing neurofunctional deficits in ADHD (Schweitzer *et al.* 2004; Konrad *et al.* 2007; Schulz *et al.* 2012). However, varying doses of MPH have also been found to normalize neurofunctional deficits in ADHD (Vaidya *et al.* 1998; Bush *et al.* 2008; Rubia *et al.* 2009*a*; Posner *et al.* 2011). Only one N-back study provided the average MPH dose to which their participant group was exposed (Kobel *et al.* 2009). To account for the precise impact of MPH exposure upon fMRI results, future studies should outline not only the average length of exposure to MPH, but also the dose of MPH that the ADHD population under examination has been treated with. ADHD participant exposure to non-pharmacological interventions have also been linked to normalizing neural function (Hoekzema *et al.* 2010). As non-pharmacological treatment history was omitted across meta-analysed studies, future studies should document this information as it may account for variability in fMRI findings.

Effects of age and development

We found a link between older age in childhood ADHD and increased right inferior frontal gyrus activity, but this should be interpreted cautiously as the age range within Stop task studies only spanned adolescence with the exception of one adult study.

Differences between adult and child studies across Go/no-go task studies may be due to developmental differences between groups (Fassbender & Schweitzer, 2006). ADHD adults displayed less left medial frontal gyrus and right inferior parietal lobule activity than healthy adults. Reduced activation in the left medial frontal gyrus in adult ADHD studies is noteworthy, as hypoactivity across these regions has been linked to heightened negative affect in those with and without major depressive disorder (Zhou *et al.* 2010). This finding suggests a tentative link between the neuropathology of ADHD and co-morbid affective disorder development, which occurs in up to 50% of adult ADHD cases (Kessler *et al.* 2005, 2010; Frodl, 2010).

In studies investigating children, the ADHD participants activated the right superior frontal gyrus less than controls, whereas they activated the right middle frontal gyrus more than controls. Amongst children with ADHD, a lag in cortical maturation affecting the development of higher-order association areas involved in more advanced attentional control has been proposed which may account for our finding as control children activated a superior frontal area (Fassbender *et al.* 2006).

Differences highlighted between ADHD in adults and ADHD in children with regards to fMRI findings may be due to the clinical presentation of ADHD changing with increasing age (Faraone *et al.* 2006); the hyperactive and impulsive symptoms of childhood ADHD become less pronounced, while inattentive symptoms persist (Biederman *et al.* 2000), which may cause dependence upon neural regions to vary across age groups (Greydanus *et al.* 2007).

Effect of IQ

Future work is required to investigate the link between IQ and the functional alterations between ADHD participants and controls in the right medial frontal gyrus in Stop task studies and the right caudate in Go/no-go studies. IQ levels for ADHD participants were at median level or above. A developmentally stable global reduction in cerebral grey matter volume for ADHD participants of above median IQ compared with controls of equal IQ may account for our finding (De Zeeuw *et al.* 2012). It must be noted that studies with greater IQ differences between ADHD participants and controls also had a higher percentage of combined-type ADHD participants; therefore neural differences generated by IQ differences in these ADHD participants may have been influenced by ADHD subtype. ADHD subtype may inherently skew the IQ score, as ADHD severity may hamper compliance with the IQ test itself due to inattention or impatience (Rubia *et al.* 2011*b*). Thus, IQ score may be underestimated and be more influenced by ADHD severity than intellectual ability (Biederman *et al.* 2012). Future studies could benefit from contrasting participants of 'high IQ' with those of 'average IQ', so as to fully investigate how IQ modulates neural function.

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Effect of ADHD subtype

ADHD subtype may make an impact on testing outcome and present independent forms of the disorder (Rasmussen *et al.* 2004; Solanto *et al.* 2009). Consistent frontal deficits across ADHD subtypes imply homogeneous cognitive strategies involved in ADHD behavioural control (Solanto *et al.* 2009). However, our finding of a link between a high percentage of combined-type ADHD and increased left fusiform and right lingual gyrus in Go/no-go task studies along with the finding that a lower percentage of combined-type ADHD is linked to decreased right middle and medial frontal gyri in Stop task studies, demonstrates how different subtypes have specific neural attributes.

Our findings, however, do not align with the single study to date which compared ADHD subtypes using an fMRI cognitive task paradigm. Solanto *et al.* (2009) found that the bilateral middle frontal gyrus was more activated in children with ADHD predominantly inattentive-type (ADHD-PI) than those with combined-type ADHD. Conversely, children with combined-type ADHD activated the bilateral medial occipital lobe to a greater extent than children with ADHD-PI (Solanto *et al.* 2009).

This divergence may be due to our result being borne of a regression with a minute number of non-combined-type ADHD participants as opposed to a direct comparison. None of the meta-analysed studies explicitly examined differences between individuals of varying ADHD subtype (Booth *et al.* 2005; Schulz *et al.* 2005; Durston *et al.* 2006). As there were only four participants with hyperactive impulsive-type ADHD and 30 participants with inattentive-type ADHD across all studies, distinguishing hyperactive impulsive and inattentive-type from combined-type ADHD was not possible in the present meta-analysis. However, this could be an interesting objective for future fMRI studies.

Previous meta-analyses

Interestingly our findings aligned with a recent meta-analysis which parcellated fMRI findings into large-scale neural networks (Cortese *et al.* 2012). Cortese *et al.* (2012) found that the level of frontal region deactivation compared with controls coincided with increased task complexity, which could also account for differences we observed between groups particularly in Go/no-go studies (Huizenga *et al.* 2009; Cortese *et al.* 2012). Although we did not find significant DLPFC differences between groups across all studies similar to Hart *et al.* (2013); we did find that a history of treatment potentially normalized frontal deficits in activity similar to the finding by Hart *et al.* (2012) that right DLPFC activation was reduced in medication-naive patients but normal in long-term stimulant-medicated patients relative to controls (Hart *et al.* 2012).

Limitations

A limitation of this meta-analysis is the cross-sectional nature of all of the studies included. While differences were observed between groups, it is not entirely possible to deduce the longitudinal effects from childhood to adulthood based upon cross-sectional studies. Also peak-based meta-analyses are based on coordinates from published studies rather than raw statistical brain maps, which limit a complete analysis of data generated from participants (Hart *et al.* 2012; Radua *et al.* 2012).

Conclusion

In conclusion, this meta-analysis highlighted some consistent findings within ADHD research. Frontal region deficits across tasks and age groups within this analysis suggest a consistent pattern of ADHD neural dysfunction. Equally, this meta-analysis demonstrated that fMRI results may be ascribable to the normalizing effect of varying treatment history, unaccounted for fully in many studies. Our findings also signify a need for segregated examination and contrast across study populations of levels of MPH exposure, prior non-pharmacological treatment, IQ level and ADHD subtype in future studies. This is necessary in order to formulate a successful automated diagnosis of ADHD using the neural correlates derived from imaging studies free from confounding factors, which would have fundamental consequences upon the public health impact of the disease (Eloyan *et al.* 2012).

Supplementary material

For supplementary material accompanying this paper, visit http://dx.doi.org/10.1017/S0033291713001037.

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Declaration of Interest

None.

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