The Journal of Mind and Behavior
Summer 2018, Volume 39, Number 3
Pages 205–228
ISSN 0271–0137

Broken Brains or Flawed Studies? An Update on Leo and Cohen's Critical Review of ADHD Neuroimaging

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This systematic review sought to examine neuroimaging results on Attention Deficit Hyperactivity Disorder (ADHD) published between 2003 and 2015, paying special attention to the major confound of prior medication use first brought to attention by Leo and Cohen (2003) and subsequently acknowledged in the ADHD literature. Neuroimaging studies comparing children and adolescents with ADHD were identified through searches in Web of Science (BIOSIS, Web of Science Core Collection, MEDLINE), PsychINFO, and EMBASE. All studies focusing on neuroimaging and ADHD were selected for consideration (n=62). Forty studies (64.5%) still included pre-medicated samples despite the confound and eight studies (13%) did not provide information to determine this, leaving only 14 studies with medication-free participants to be analysed. The findings on reported differences in physical systems and in electrical activation between ADHD participants and controls were inconsistent and, in part, short on methodological rigour. Despite technological advances, the current state of research suggests that the understanding of neurobiological underpinnings of ADHD and the significance of that research for individuals diagnosed with ADHD has not advanced since the Leo and Cohen review.

Keywords: ADHD, neuroimaging, Leo and Cohen, medication-naive

Attention Deficit Hyperactivity Disorder (ADHD) is characterised by developmentally inappropriate symptoms of hyperactivity, impulsivity, and inattentiveness

We would like to thank Raymond Russ and the anonymous reviewers for their insightful critique on our initial draft of this article. Correspondence concerning this article should be sent to Charles Marley, University of Edinburgh, School of Health in Social Science, Section of Clinical and Health Psychology, Teviot Place, Edinburgh, EH8 9AG Scotland. Email: charles.marley@ed.ac.uk

(American Psychiatric Association, 2013). It is considered to be the most prevalent child psychiatric disorder worldwide (Dubnov–Raz, Khoury, Wright, Raz, and Berger, 2014), affecting 5–7% of young people (Polanczyk and Rohde, 2007; Willcutt, 2012). That said, accurately accounting for ADHD's widespread expression is complicated by ambiguous symptoms, frequent comorbidities, as well as the presence of many of ADHD's defining behaviours among the general population (National Collaborating Centre for Mental Health, 2009). Researchers are increasingly discussing the nature of this condition (Buitelaar and Rothenberger, 2004), and even its very existence has been questioned in some quarters (Saul, 2014). Reliable diagnostic criteria are of critical importance in such a climate (Campbell, Shaw, and Gilliom, 2000); however, the arbitrary cut-off scores and the vague terminology used to distinguish between healthy and pathological levels of symptom expression undermine the criteria (National Collaborating Centre for Mental Health, 2009) and has led numerous commentators to argue that this has contributed to an over-diagnosing of children (Chilakamarri, Filkowski, and Ghaemi, 2011; Jensen, 2002; LeFever, Arcona, and Antonuccio, 2003). In addition to these criticisms, the prevailing diagnostic system most commonly used to guide ADHD diagnosis, the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, fifth edition, 2013), has been criticised for lacking empirical grounding (Frances, 2013; Kirschner, 2013) and thus has failed in the DSM committee's aspiration for the development of a pathophysiological-based classification system (Carroll, 2013), with no conclusive evidence of biomarkers for ADHD or any other psychiatric conditions offered as yet (Jaffee, 2018; Thome et al., 2012).

This disillusion, along with the appropriate technological advances, have fuelled the popularity of more rigorous methods of establishing the specific biological markers of disorder. The most prominent of these approaches are neuroimaging studies, with numerous research and review papers suggesting a dysfunction in fronto-striatal and fronto-parietal networks (Bush, Valera, and Seidman, 2005; Castellanos et al., 2002; Durston et al., 2003; Giedd, Blumenthal, Molloy, and Castellanos, 2001; Sowell et al., 2003) and reduced volume of the prefrontal cortex, cerebellum, and cerebrum (Almeida et al., 2010; Bledsoe, Semrud–Clikeman, and Pliszka, 2013; Mostofsky, Cooper, Kates, Denckla, and Kaufmann, 2002; Soliva, Moreno et al., 2010) as being common across ADHD-diagnosed patients. The recently developed diffusion tensor imaging (DTI) technique has added to these findings, indicating possible variations in functional connectivity in fronto-striatal and cerebellar circuitry when ADHD subjects are compared to healthy controls (Fall, Querne, Le Moing, and Berquin, 2015; Silk, Vance, Rinehart, Bradshaw, and Cunnington, 2009a).

While the findings of these studies appear authoritative, they have received considerable criticism due to several methodological flaws. As an example, a systematic review of over thirty neuroimaging studies by Giedd et al. (2001) concluded that there are physiological differences between the brains of children

diagnosed with ADHD as compared to a non-ADHD sample. However, Leo and Cohen (2003) reconsidered the review. The main thrust of Leo and Cohen's criticism was that Giedd et al. (2001) failed to consider a major confounding variable: that the ADHD samples had been medicated over months or years prior to inclusion in a number of the reviewed studies. This important omission led Leo and Cohen to argue that the evidence suggesting that ADHD is a neurobiological condition cannot be assumed. In support of their position, the authors highlighted the effects of drug administration from animal studies, arguing that the anatomical differences revealed by neuroimaging could equally be the impact of stimulant medication use as opposed to ADHD-specific abnormalities (Breggin, 2000; Sproson, Chantrey, Hollis, Marsden, and Fone, 2001). However, this is not to say that neuroimaging studies involving medication-naive samples have not been conducted; for example, in one study involving a medication-naive sample (Castellanos et al., 2002), the control group participants were more than two years older, as well as heavier and taller than the ADHD participants, suggesting that the differences located could be explained by maturity and growth. As such, the main criticism of neuroimaging studies still stands: that it is impossible to disentangle cause and effect (Leo and Cohen, 2003).

As neuroimaging studies constitute the bulk of the evidence for the prevailing neurodevelopmental explanation of ADHD, it is imperative that the findings are reliable and valid and drawn from methodologically robust studies. This imperative is further emphasised by the exponential rise in ADHD diagnosis globally and its associated increase in stimulant medication prescriptions (Bachmann et al, 2017; Davidovitch, Koren, Fund, Shrem, and Porath, 2017; Nyarko et al, 2017). Given that treating children and young people with medication is associated with severe side-effects (Greene, Kerr, and Braitberg, 2008; Higgins, 2009; Holmskov et al., 2017; Kovshoff et al., 2016; Sparks and Duncan, 2004; Swanson et al., 2007), that the authority for this approach is underpinned by methodologically flawed studies is a profound ethical concern. Utilisation of a pre-medicated sample has been fully acknowledged within the neuroimaging literature as a major confound as a result of the Leo and Cohen review (Smith, Taylor, Brammer, Toone, and Rubia, 2006). Our review engages with this important issue by updating the Leo and Cohen (2003) study by systematically reviewing neuroimaging studies from 2003 onwards. We also consider sample matching of the studies that have corrected this methodological limitation in light of the other major confound of maturity and growth highlighted by Leo and Cohen. A final aim of our review is to synthesise and contrast the reported findings of the included studies.

Method

An extensive search for neuroimaging studies comparing children diagnosed with ADHD with healthy controls, published between 2003 and 2015,

was conducted using the following databases: BIOSIS, Web of Science Core Collection, EMBASE, and psychINFO. The keyword search terms included were: Attention Deficit Hyperactivity Disorder (ADHD), neuroimaging, brain scan, Computerized Tomography (CT), Magnetic Resonance Imaging (MRI), Single-Photon Emission Computed Tomography (SPECT), and Positron Emission Tomography (PET).

Neuroimaging studies comparing children and/or adolescents (5–18 years) with ADHD and matched controls were included. Studies in which the diagnosis of ADHD was performed according to standard criteria (DSM or ICD) were retained. Studies including participants with any comorbidities (including conduct disorder or oppositional defiant disorder) were excluded. Reviews, books, case reports, theses, and abstracts of conference papers were also excluded from the original search. At this stage, 3715 papers were sourced. After removing the duplicates and irrelevant papers, 253 full-text articles were screened. Applying the inclusion and exclusion criteria yielded a total of 62 studies. Details of the studies that met the inclusion criteria are provided in the results section. A review of the selection process is displayed in Figure 1.

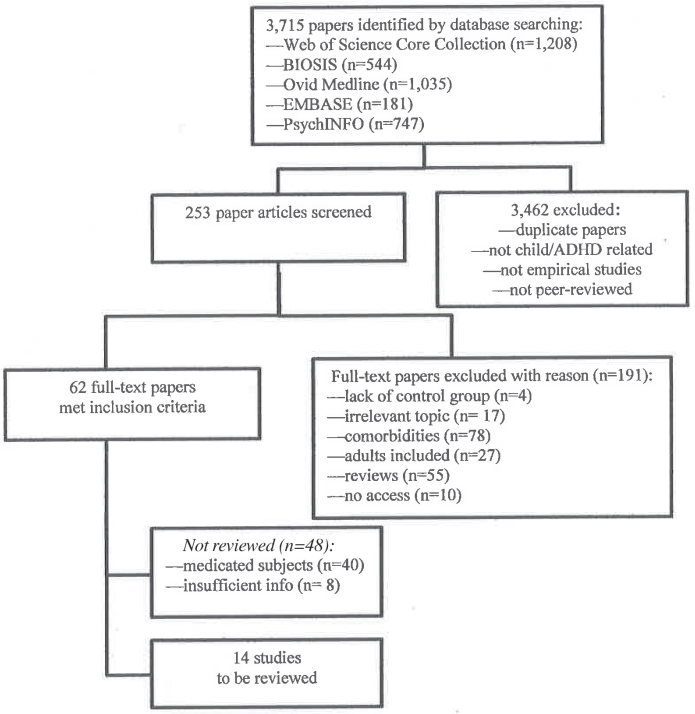

Figure 1: Literature search results.

Results

Prior-Medicated Sample

Of the 62 papers eligible for inclusion, 40 involved pre-medicated participants and eight failed to provide sufficient information. Six studies used the ADHD 200 database and were unable to provide specific demographic information of the participants. Two studies (Li et al., 2007; Wang, Jiang, Cao, and Wang, 2007) did not mention prior medication use. In addition, 61 studies excluded for comorbidities also continued to use a pre-medicated sample, meaning 101 neuroimaging studies regarding ADHD since the original Leo and Cohen study have continued to use a pre-medicated sample. We will return to this point in the discussion. An overview of the excluded studies is presented in Table 1.

Table 1

Studies Using Pre-Medicated Samples or Not Providing Sufficient Information to Review

Fulfilled Inclusion Criteria but Medicated (N=40)	Insufficient Information on Demographics and Medication (N=8)
Bledsoe, Semrud–Clikeman, and Pliszka, 2011	Cheng et al., 2012 (ADHD 200)
Bledsoe, Semrud–Clikeman, and Pliszka, 2013	Colby et al., 2012 (ADHD 200)
Booth et al., 2015	Eloyan et al., 2012 (ADHD 200)
Carmona et al., 2015	Kessler et al., 2014 (ADHD 200)
Chabernaud et al., 2012	Siqueira et al., 2014 (ADHD 200)
Courvoisie, Hooper, Fine, Kwock, and Castillo, 2004	Sripada et al., 2014 (ADHD 200)
Dias et al., 2015	Li et al., 2007
Fair et al., 2010	Wang et al., 2007
Fan, Gau, and Chou, 2014	
Fassbender et al., 2009	
Fassbender et al., 2011	
Garvey et al., 2005	
Li et al., 2012	
Liotti, Pliszka, Perez, Kothmann, and Woldorff, 2005	
Lopez–Larson, King, Terry, McGlade, and Yurgelun–Todd, 2012	
Ma et al., 2012	
McAlonan et al., 2009	
Mostofsky, Cooper, Kater. Denckla, Kaufmann, 2002	
Mostofsky et al., 2006	
Murias, Swanson, and Srinivasan, 2006	
Paloyelis, Mehta, Faraone, Asherson, and Kuntsi, 2012	
Peng, Lin, Zhang, and Wang, 2013	
Pineda et al., 2002	
Poissant, Mendrek, and Senhadji, 2014	

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Table 1 (continued)

Posner et al., 2011
Qiu et al., 2009
Shaw et al., 2009
Silk, Vance, Rinehart, Bradshaw, and Cunnington, 2009a
Silk, Vance, Rinehart, Bradshaw, and Cunnington, 2009b
Soliva, Fauquet et al., 2010
Soliva, Moreno et al., 2010
Sowell et al., 2003
Stevens, Pearlson, and Kiehl, 2007
Tamm, Menon, and Reiss, 2006
Tamm, Menon, Ringel, and Reiss, 2004
Tian et al., 2006
Tian et al., 2008
Tomasi and Volkow, 2012
Tremols et al., 2008
Xia, Foxe, Sroubek, Branch, and Li, 2014

Medication Controlled Studies

The majority of the reviewed studies are underpowered: ten out of 14 studies fell significantly below the recommended sample size of 25 required for an accurate activation map (Desmond and Glover, 2002; Fall et al., 2015; Fayed, Modrego, Castillo, and Dávila, 2007; Fernández et al., 2009; Massat et al., 2012; Murphy and Garavan, 2004; Pueyo et al., 2003; Silk et al., 2005; Silk, Vance, Rinehart, Bradshaw, and Cunnington, 2008; Spalletta et al., 2001; Vance et al., 2007; Weber, Lütschg, and Fahnenstich, 2005). The largest sample size involved forty ADHD children (Kim, Lee, Shin, Cho, and Lee, 2002); however, due to the ethical concern of including healthy controls for SPECT imaging, children who had previously received SPECT for headaches were used as controls, limiting the control group sample to seventeen. A discrepancy in experimental group and control group sample size was noted in an additional four studies (Fayed et al., 2007; Li, Li et al., 2014; Massat et al., 2012; Weber et al., 2005) with three studies also underpowered (Fayed et al., 2007; Massat et al., 2012; Weber et al., 2005).

In terms of matched control samples, all studies adequately controlled for confounds such as comorbidities, utilising only samples with an ADHD diagnosis. The impact of differing brain-region activation between left and right handedness (Cuzzocreo et al., 2009) was controlled by utilising only right-handed participants; in doing so, however, all studies inadvertently limited the external validity (i.e., generalization) of their findings. Further, experimental groups were insufficiently matched in age in the majority of studies. A number of studies tested for differences in age between groups, and reported no significant differences, but none of the studies compared the age range of groups with the mean age of the

groups. As an example, in the study by Fayed et al. (2007), the age range of the experimental sample was 6–16 and the control group was 4–12; there may not be significant differences in the mean age of the group, but there is significant variation in age within and between samples, which will be discussed below. This observation is worth considering especially in the studies with apparently less variance in age. For example, in the study by Pueyo et al. (2003), participant ages were not provided, but by using the standard deviation, we can calculate that 99.7% (assuming normal distribution) of the experimental group fell between the ages of 12.6–17.58, an age range of almost 5 years, while in the control group the age range was 3.48 years. Given that adolescence is a time period of substantial changes in the brain (Dahl, 2004), not controlling for age range undermines claims that differences between participant groups highlight a neurological basis for ADHD.

Finally, the various subtypes of ADHD are often not explored. One would assume that, given the manifestly different presentations between the subtypes (ADHD-Combined and ADHD-Inattentive), different brain regions or systems are involved, which would require closer matching across samples. This position appears to be substantiated by Fair et al. (2013) who argued that, whilst the different subtypes possess some overlapping aspects, they also display unique patterns of atypical connectivity. However, the only study to utilise differentiated samples (ADHD-I and ADHD-combined) was Lei et al. (2014). Six studies only used the ADHD-combined subtype (Fall et al., 2015; Fernández et al., 2009; Massat et al., 2012; Silk et al., 2005, 2008; Vance et al., 2007), with the remaining seven studies using a mixed subtype sample and not providing sufficient information on which to assess this issue. An overview of the sample characteristics of reviewed studies can be found in Table 2.

Synthesis of Findings

According to the reviewed articles, several brain regions (frontal, parietal, occipital, cerebellum, striatum, and basal ganglia) are associated with ADHD. However, the brain regions and associated dysfunction implicated in the expression of ADHD are inconsistent across the reviewed studies, with the brain regions implicated differing across different imaging technologies as well differing among studies using the same imaging technology. An overview of reviewed study findings can be viewed in Table 3.

Frontal lobe. The one study to utilise structural MRI (Pueyo et al., 2003) found that ADHD participants had a higher degree of myelination in the right frontal lobe than did controls. Lei et al.'s (2014) results suggest reduced axial and radial diffusivity in the left middle frontal gyrus. Spalletta et al.'s (2001) finding of decreased regional cerebral blood flow (rCBF) in the left prefrontal region seems in accordance with the oxygenated and deoxygenated haemoglobin imbalance reported by

Table 2

Breakdown of Included Study Sample Characteristics

Study	Sample Description*		
	ADHD	Control	ADHD Group Constitution
Fall et al., 2015	N = 11 M/F = 10/1 Mean age: No details SD: No details Range: No details	N = 11 M/F = 8/3 Mean age: No details SD: No details Range: No details	11 ADHD-Combined
Fayed et al., 2007	N = 22 M/F = 18/4 Mean age: 9 SD: 2.91 Range: 6–16	N = 8 M/F = 4/4 Mean age: 7 SD: 3 Range: 4–12	No details
Fernández et al., 2009	N = 14 M/F = 14/0 Mean age: 9.64 SD: 1.04 Range: 8–12	N = 17 M/F = 17/4 Mean age: 10.36 SD: 1.48 Range: 8–13	14 ADHD-Combined
Kim et al., 2002	N = 40 M/F = 32/8 Mean age: 9.7 SD: 2.1 Range: 8–12	N = 17 M/F = 15/2 Mean age: 10.4 SD: 2.2 Range: 8–12	No details
Lei et al., 2014 (Three groups — two experimental and one control group)	N = 28 M/F = 25/3 Mean age: 9.3 SD: 1.3 Range: No details N = 28 M/F = 25/3 Mean age: 9.3 SD: 1.3 Range: No details	N =28 M/F = 25/3 Mean age: 9.2 SD: 1.4 Range: No details	Group 1: 28 ADHD-Inattentive Group 2: 28 ADHD-Combined
Li, He et al., 2014	N = 33 M/F = 33/0 Mean age: 10.1 SD: 2.6 Range: 6–16	N = 32 M/F = 32/0 Mean age: 10.9 SD: 2.6 Range: 8–16	22 ADHD-Combined 11 ADHD-Inattentive
Li, Li et al., 2014	N = 33 M/F = 33/0 Mean age: 9.9 SD: 2.4 Range: 6–15	N = 27 M/F = 27/0 Mean age: 10.9 SD: 2.7 Range: 8–16	22 ADHD-Combined 11 ADHD-Inattentive

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Table 2 (continued)

Massat et al., 2012	N = 19 M/F = No details Mean age: 10.75 SD: 1.31 Range: No details	N = 14 M/F = No details Mean age: 10.05 SD: 1.28 Range: No details	19 ADHD-Combined
Pueyo et al., 2003	N = 11 M/F = 8/3 Mean age: 15.09 SD: 0.83 Range: 14–17	N = 20 M/F = 15/5 Mean age: 14.85 SD: 0.58 Range: No details	No details
Silk et al., 2005	N = 7 M/F = 7/0 Mean age: 14.38 SD: 1.85 Range: 11–17	N = 7 M/F = 7/0 Mean age: 14.56 SD: 1.77 Range: No details	ADHD-Combined
Silk et al., 2008	N = 12 M/F = 12/0 Mean age: 11.15 SD: 1.53 Range: No details	N = 12 M/F = 12/0 Mean age: 11.09 SD: 1.50 Range: No details	12 ADHD-Combined
Spalletta et al., 2001	N = 8 M/F = No details Mean age: 9.4 SD: 2.0 Range: 6–12	N = 8 M/F = No details Mean age: 9.0 SD: 2.1 Range: 6–12	7 ADHD-Combined 1 ADHD-Inattentive
Vance et al., 2007	N = 12 M/F = No details Mean age: 11.1 SD: 1.5 Range: 8–12	N = 12 M/F = No details Mean age: 10.2 SD: 1.3 Range: No details	12 ADHD-Combined
Weber et al., 2005	N = 11 M/F = No details Mean age: 10.4 SD: 1.2 Range: No details	N = 9 M/F = No details Mean age: 11.3 SD: 1.3 Range: No details	7 ADHD-Hyperactive 4 ADHD-Inattentive

* Effect sizes for the reviewed studies are not provided as it would appear that effect sizes are not normally calculated for traditional neuroimaging studies (Reddan, Lindquist, and Wager, 2017). It is possible to calculate effect sizes for the difference between groups in relation to tasks performed as part of the neuroimaging process (i.e., flanker task) but this would only be for the studies that utilised a task (not all did) and for the those that provided enough information (not all did).

Weber et al. (2005). The indicated differences in N-acetylasparate/creatine ratios in the right prefrontal corticosubcortical regions (Fayed et al., 2007) suggest a chemical imbalance.

The majority of studies included utilised fMRI. The three studies that focused on the frontal lobe reported general reduced activation in ADHD participants (Kim et al., 2002; Silk et al., 2005; Vance et al., 2007). Li, He et al. (2014) found interhemispheric differences, with lower activation in the left orbitofrontal cortex and the left ventral superior frontal gyrus and higher activation in the right dorsal superior frontal gyrus for ADHD participants. The results of the Silk et al. (2005) study indicate a lower activation in the left prefrontal cortex and superior and bilateral inferior gyri and higher activation in the medial superior prefrontal cortex.

Table 3

Overview of Brain Regions Associated with ADHD

Brain Regions	Differences in Physical Systems	Differences in Electrical Activation	Studies
Frontal	more myelination in right frontal lobe	lower activation in frontal lobe	Fayed et al., 2007 Fernández et al., 2009 Kim et al., 2002
	differences in N-acetylaspartate/creatine ratios in right prefrontal corticosubcortical region	lower activation in right lateral prefrontal cortex, bilateral orbito prefrontal cortex	Lei et al., 2014 Li He et al., 2014 Pueyo et al., 2003 Silk et al., 2005 Silk et al., 2008
	decreased rCBF in left dorso lateral prefrontal cortex compared to right		Spalletta et al., 2001 Vance et al., 2007 Weber et al., 2005
	decreased radial and axial diffusivity in the left middle frontal gyrus in ADHD-I	lower activation in inferior frontal gyrus	
	imbalance between oxygenated and deoxygenated haemoglobin during the short- and extended-attention tasks compared to lateralized oxygen consumption in left prefrontal cortex in controls	lower activation in left orbitofrontal cortex and the left ventral superior frontal gyrus and higher activation in the right dorsal superior frontal gyrus	
		lower activation in left prefrontal cortex and in superior and bilateral inferior frontal gyri and higher activation in medial superior prefrontal cortex	

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Table 3 (continued)

Parietal	increased blood flow in parietal lobe	lower activation in bilateral inferior parietal gyri	Kim et al., 2002 Massat et al., 2012 Silk et al., 2005
		lower activation in right inferior parietal	Silk et al., 2008 Vance et al., 2007
		lower activation in posterior parietal regions: left supramarginal gyrus, bilateral precuneus, and inferior parietal lobule	
Occipital	increased blood flow in occipital lobe	decreased bilateral activation	Kim et al., 2002 Lei et al., 2014 Massat et al., 2012
	more myelination in left posterior compared to right	less activation in right parieto-occipital areas (cuneus and precuneus)	Pueyo et al., 2003 Silk et al., 2008 Vance et al., 2007
	increased radial diffusivity in left occipital (in ADHD-I)		
Temporal	reduced axial diffusivity in left middle temporal (in ADHD-I) and increased in the right middle temporal (in ADHD-CT)	temporal lobe less active	Kim et al., 2002 Lei et al., 2014
		higher activation in right hippocampus	Li, Li et al., 2014 Silk et al., 2005 Silk et al., 2008
	increased radial diffusivity in left superior temporal gyrus (in ADHD- I and ADHD-CT)	lower activation in right middle temporal cortex	
	decreased fractional aniostrophy in left parahippocampal gyrus (in ADHD- CT)	higher activation in the left middle and superior temporal gyri	
		lower activation in bilateral superior temporal gyrus	
Striatum and Basal Ganglia	increased axial diffusivity in the right caudate (in ADHD-I and ADHD-CT)	decreased activation in bilateral caudate nuclei	Fall et al., 2015 Lei et al., 2014 Li, He et al., 2014 Li, Li et al., 2014
		lower activation in right caudate nucleus	Massat et al., 2012 Silk et al., 2005 Silk et al., 2008
	reduced volume and higher diffusivity in ADHD patients compared to controls, especially in caudate, thalamus, and putamen	higher activation in bilateral globus pallidus	Vance et al., 2007
Cerebellum	decreased activation in cerebellum		Massat et al., 2012 Silk et al., 2008

Parietal, occipital, and temporal lobes. Kim et al. (2002) reported increased blood flow in the parietal lobe, while reduced activation was found either in the right inferior parietal lobe (Silk et al., 2005; Vance et al., 2007) or bilaterally in inferior parietal gyri (Massat et al., 2012; Silk et al., 2008). Silk et al. (2008) reported an overall reduction of activation in the posterior parietal regions. Less activation was also displayed in the bilateral occipital (Massat et al., 2012; Silk et al., 2008) and the right parieto-occipital areas (Vance et al., 2007). Interhemispheric differences were found in the posterior occipital region, with a more myelinated left side (Pueyo et al., 2003). Lei et al. (2014) reported increased radial diffusivity in the left occipital region. The temporal lobe was also found to be less active (Silk et al., 2008). Lei et al. (2014), who compared children with ADHD-I, ADHD-CT, and healthy controls, found reduced axial diffusivity in the left middle temporal in the ADHD-I group and in the right middle temporal in the ADHD-CT group. Kim et al. (2002) found lower activation in the right middle temporal cortex, while Silk et al. (2005) found higher activation in the left middle and superior temporal cortex. Higher activation was reported in the right hippocampus (Li, Li et al., 2014; Silk et al., 2008) and decreased fractional anisotropy in the left parahippocampal gyrus (Lei et al., 2014).

Striatum, basal ganglia, and cerebellum. Decreased activation of white matter was found in the bilateral caudate nuclei in one study (Massat et al., 2012) and only in the right caudate nucleus in another (Vance et al., 2007). Two other studies found higher activation in bilateral globus pallidus (Li, He et al., 2014; Li, Li et al., 2014). Fall et al. (2015) reported reduced volume and higher diffusivity in ADHD patients compared to controls, especially in caudate, thalamus, and putamen. Finally, decreased activation was noted in the cerebellum (Massat et al., 2012).

Discussion

In light of the criticisms raised at the beginning of this paper, our study aimed to update the Leo and Cohen review of pre-medicated samples in ADHD neuroimaging studies. Since the original review, use of pre-medicated samples has been fully acknowledge within the neuroimaging literature as a confound (Smith et al., 2006), meaning studies from this point onwards must control for this variable for findings to be considered empirically robust. From the initial papers deemed relevant, 78 included participants with comorbidities. Admittedly, considering the frequency of comorbid conduct disorder or oppositional defiant disorder (Burke, Loeber, and Birmaher, 2002; Ollendick, Jarrett, Grills–Taquechel, Hovey, and Wolff, 2008), participant recruitment can be challenging; however, given these comorbidities are behaviourally indistinguishable from ADHD (National Collaborating Centre for Mental Health, 2009), it is imperative that studies locate "pure" ADHD in order to provide a sound basis for treatment (Wang et al., 2012).

The most surprising finding from our review was the number of studies continuing to use pre-medicated samples. From the 62 studies that met the inclusion

criteria, 40 continued to use pre-medicated samples. In addition to the 40 studies that met the inclusion criteria, the 61 studies that excluded for comorbidities continued to use pre-medicated samples. This finding is perplexing considering the obviousness of the confound and its recognition as such in the neuroimaging literature. The most frequently offered rationale for inclusion was that all participants were withheld from medication treatment for a seemingly arbitrary 24, 48, or three-day period. However, there is no comprehensive study to date that offers an authoritative time-period after which a participant can be considered medication-free. Until then, studies claiming to include medication-free participants, based on hours of withheld medication, introduce the possibility of withdrawal symptoms as an additional problem (Leo, 2004).

A further issue was the number of studies that ignored this serious confound, with eleven studies not mentioning participant medication status (Cheng, Ji, Zhang, and Feng, 2012; Colby et al., 2012; Eloyan et al., 2012; Kessler, Angstadt, Welsh, and Sripada, 2014; Kim et al., 2010; Li et al., 2007; Siqueira, Biazoli, Comfort, Rohde, and Sato, 2014; Sripada Kessler, and Angstadt, 2014; Wang et al., 2007, 2009; Wellington, Semrud–Clikeman, Gregory, Murphy, and Lancaster, 2006). Six of these studies used their application of the ADHD 200 database as a rationale for insufficient demographic details (including medication information) [Cheng et al., 2012; Colby et al., 2012; Eloyan et al., 2012; Kessler et al., 2014; Siqueira et al., 2014; Sripada et al. 2014], despite the ADHD 200 agreement stating that "*the specific datasets included in analyses be specified appropriately*" (Milham, Fair, Mennes, and Motofsky, 2012), placing the onus on researchers to provide the demographic information for their sample. Given the problem of using a pre-medicated sample, and the resulting impact on the reliability and validity of the findings, we did not feel these papers warranted further analysis, leaving only 14 study findings to be extrapolated and considered in more detail.

A further major methodological limitation that affected the reviewed studies was small sample sizes, with more than half the studies (8/14) using sample sizes below 15, which limits power, and increases the likelihood of type I errors (Murphy and Garavan, 2005). Jennings and Van Horn (2012) raised this issue in their review of publication bias in neuroimaging research. Due to the number of studies with small sample sizes, Jennings and Van Horn expected to find a large number of studies supporting the null hypothesis or reporting non-significant findings due to lack of power, but this was not the case. The conclusion offered by Jennings and Van Horn was that this indicated publication bias towards positive results. However, given the lack of power of these studies, how these positive results were achieved in the first-place warrants consideration. To answer this, one needs to look to the influence of confounding variables, such as age differences between samples (Ioannidis, 2011), undifferentiated disorder subtypes in the experimental group (Fair et al., 2013), the considerable age range of the sample, multiple comparison statistical correction procedures (Bennett, Wolford, and

Miller, 2009), and untested statistical procedures within fMRI software (Eklund, Nichols, and Knutsson, 2016).

The influence of age range on results in neuroimaging studies was highlighted in the original Leo and Cohen review as problematic, as results could indicate the influence of maturation on the brain. Our review took this important point further, noting that age range varied considerably, with some studies having as large as a ten-year gap between the youngest and oldest child. As neuroimaging studies of typical development have indicated age-specific differences in gray and white matter (Sowell et al., 1999; Sowell, Trauner, Gamst, and Jernigan, 2002), the large variance in ages between and within participant groups raises the possibility that the positive results represent the considerable neurological growth that occurs during childhood rather than ADHD related abnormalities (Giedd et al., 1999; Samanez–Larkin and D'Esposito, 2008).

Two areas of increasing concern in neuroimaging studies are the inflation of false positive results through fMRI software increasing false positive rates (Eklund et al., 2016) and the lack of application of methods for correcting for multiple comparisons (Bennett et al., 2009). In the Eklund et al. study, the authors examined three software packages containing applied procedures for correcting multiple comparisons when using real data. Prior to this point, imaging software was validated using simulated data. Eklund et al. found that the Familywise Error (FEW) corrected cluster *p*-values approach — the most commonly used approach for controlling the chance false positives results — inflated statistical significance. The application of a correction for multiple comparisons is a necessity in imaging studies due to the mass univariate approach used to create activation maps resulting in numerous statistical comparisons (Woo, Krishnan, and Wager, 2014). The FEW approach corrects at the level of the voxel, the unit of measurement used to indicate a collection of brain cells, with each voxel *p*-value measured against an arbitrarily set threshold of significance, before being combined as a cluster of voxels that form anatomical areas of interest. Woo et al. argued that the uncorrected FEW approach inflates the chances of "physiological noise" being included as voxels, rendering positive findings "useless" due to a lack of spatial specificity (2014, p. 418). Similarly, Bennett et al. (2009) raised concern about the use of arbitrary, uncorrected statistical thresholds in many fMRI studies, citing the voxel clustering correction as particularly problematic. Bennett et al. offered several approaches for managing the risk of inflated false positive results from multiple comparisons. From the 14 studies reviewed in our study, we located only four studies (Fernández et al., 2009; Li, Li et al., 2014; Massat et al., 2012; Spalletta et al., 2001) applying one of the recommended approaches. We were also unable to find information on the statistical software packages used across the 14 reviewed studies. Two of the studies (Silk et al., 2008; Vance et al., 2007) reported corrected cluster *p*-values, however, which could indicate use of the problematic software highlighted by Eklund et al. (2016). Taken together, eight of our reviewed studies

did not mention the correction procedure applied, two applied procedures known to inflate false positive results, with only four applying recommended correction procedures. Three of the four studies applying recommended correction procedures are below the recommended sample size to be considered adequately powered (Fernández et al., 2009; Massat et al., 2012; Spalletta et al., 2001) with the final study (Li, Li et al., 2014) displaying a discrepancy between experimental group and control group sample size.

A final area of weakness found in our reviewed studies was the range of methodology and technology utilised and the huge disparity in regions of the brain implicated in the disorder's expression. For instance, across the articles there were considerable variations in the statistical thresholds or the strength of the imaging magnet (Paloyelis, Mehta, Kuntsi, and Asherson, 2007). A further example is the application of the region of interest (ROI) approach. The ROI approach encourages the investigation of localised brain regions through statistical mapping that highlights voxels that are more strongly activated during one condition over another (Kriegeskorte, Simmons, Bellgowan, and Baker, 2009). In this approach, neuroimaging data are first analysed to select a subset, the region of interest, followed by a selective analysis of the subset. In most cases, the region of interest is defined by statistical mapping and the subsequent analysis is based on the same data. The approach, termed double-dipping, has been criticised for increasing the risk of distorted results through violating the assumptions of random sampling, distorting descriptive statistics, and invalidating statistical inferences (Kriegeskorte et al., 2009; Vul, Harris, Winkielman, and Pashler, 2009). The approach also appears to be wide-spread and tacitly accepted in the neuroimaging community. In one analysis of 134 studies published in five prestigious journals, the practice was found to affect 42% of studies, with a further 14% not providing enough information to rule out the use of the practice (Kriegeskorte et al., 2009).

Despite the large disparity in brain regions cited across the literature, the region most frequently suggested as connected to ADHD expression was the frontal lobe or, more specifically, the prefrontal cortex (Kim et al., 2002; Silk et al., 2005; Spalletta et al., 2001). Differences in activation observed in fMRI studies would seem to support the abnormal functioning of the frontal lobe, yet there was great variation in the more specific areas reported as well as in the laterality (e.g., lower activation in the inferior frontal gyrus and higher activation in the medial superior prefrontal cortex). Thus, it is possible that the inconsistent results indicate inter-sample variance rather than ADHD markers per se. Another region implicated by the reviewed studies was the prefrontal cortex. Considering the localisation of executive functioning, which is widely acknowledged as problematic in those diagnosed with ADHD (Barkley, 2010; Kofler, Rapport, Bolden, Sarver, and Raiker, 2010; Scheres et al., 2004), a potential dysfunction in this region is plausible. While this explanation seems straightforward and comprehensive, issues of confirmation bias urge caution, as the majority of studies

demonstrating frontal lobe dysfunction confined their focus to this region during scanning, in line with the behavioural evidence linking ADHD with executive functioning. However, by limiting scan areas, according to Murphy and Garavan (2005), the studies are increasing the risk of achieving results due to Type I errors, possible through the problematic procedure of double-dipping outlined above.

In the more recent trend of whole-head imaging, increasing areas of brain regions of those diagnosed with ADHD are considered to display volumetric or functional irregularities, complicating the understanding of the underlying neurobiology. As a result, multiple alternative explanations have been formed, with dysfunction being linked to an array of interconnected brain regions and networks; for example, the fronto-striatal network (Castellanos, 1997; Durston, 2003; Giedd et al., 2001), which, incidentally, appears also to be offered as a neurological explanation for obsessive–compulsive behaviours (Melloni, Urbistondo, Sedeño, Gelormini, Kichic, and Ibanez, 2012). However, with no set image of a baseline "normal" brain, what are considered volumetric abnormalities may represent individual differences, or the impact on the brain of multiple environmental variables, rather than holistic differences between populations. For example, the impact of previous drug treatments, previous inpatient status, or differences in age and/or gender, parameters which are difficult to control efficiently, have been connected to volumetric differences (Ioannidis, 2011).

A major individual difference that appears not to have been considered by any of our reviewed studies was temperament, which has been shown to produce different activation maps across temperamental styles (Bierzynska et al., 2016; Crone and Elzinga, 2015; Fox, Henderson, and Marshall, 2001; Henderson and Wachs, 2007; Nigg, 2006; Stadler et al., 2007). As such, the impact of temperament on activation maps has been indicated as an important consideration for future imaging studies (Bierzynska et al., 2016). Additionally, the wide range of analytical techniques utilised across imaging studies make the consolidation of these multiple findings more difficult. Even if there was consistency in the abnormalities found, directionality cannot be assumed, as these measures may simply reflect reactivity variations (Bierzynska et al., 2016).

Conclusion

It appears that premature conclusions regarding the neurobiological underpinning of ADHD are still being reported as hard scientific evidence. The original review by Leo and Cohen (2003) asked important questions of the neuroimaging evidence for ADHD, thus the continued presence of the same methodological limitations and the continued lack of consistent findings in recent imaging studies is rather concerning. It may be that the technical nature of neuroimaging studies, and the highly scientific language associated with the techniques, deflects critical consideration. This specific issue has led one critic to coin the term "biobabble" to describe

the language of ADHD neuroimaging studies (Timimi, 2005). Given the side effects associated with the ADHD treatment sanctioned by neurobiological explanations, it is of utmost importance that neuroimaging studies consider their methodological limitations as pointed out in the original Leo and Cohen review, and that future neuroimaging studies continue to be critically examined to ensure their adequacy.

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