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Neuroimaging and ADHD: fMRI, PET, DTI Findings, and Methodological Limitations

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Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by pervasive and developmentally inappropriate levels of inattention, impulsivity, and hyperactivity. There is no conclusive cause of ADHD although a number of etiologic theories have been advanced. Research across neuroanatomical, neurochemical, and genetic disciplines collectively support a physiological basis for ADHD and, within the past decade, the number of neuroimaging studies concerning ADHD has increased exponentially. The current selective review summarizes research findings concerning ADHD using functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and diffusion tensor imaging (DTI). Although these technologies and studies offer promise in helping to better understand the physiologic underpinnings of ADHD, they are not without methodological problems, including inadequate sensitivity and specificity for psychiatric disorders. Consequently, neuroimaging technology, in its current state of development, should not be used to inform clinical practice.

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by pervasive and developmentally inappropriate levels of inattention, impulsivity, and hyperactivity (American Psychiatric Association, 2000). ADHD affects approximately 3% to 7% of the school-age population and the majority of individuals continue to express significant symptoms throughout adolescence and into adulthood (Lara et al., 2009). Currently, the American Psychiatric Association recognizes three subtypes of ADHD depending on the presence or absence attention, impulsivity and hyperactivity symptoms: ADHD Combined Type, ADHD Predominately Inattentive Type, and ADHD Predominantly Hyperactive-Impulsive Type. ADHD symptoms cause significant impairments at home and school and studies have found that children with ADHD are more likely to have greater difficulties with their peers and to be rejected socially than typically developing classmates, and teachers are more likely to perceive a child with an ADHD label less favorably with respect to intelligence, personality, and behavior (Alqahani, 2010; Barkle, 2006; Batzle, Weyandt, Janusis, & DeVietti, 2010; Hinshaw, 2002). Children with ADHD are also more likely to have lower grades, reading problems, and poorer scores on standardized tests, are at a higher risk for dropping-out of high school, and are less likely than their peers to pursue post-secondary education (Barbareasi, Katusic, Colligan, Weaver, & Jacobsen,

2007; DuPaul & Weyandt, 2009; Loe & Feldman, 2007). As adults, these individuals tend to complete fewer years of education, and have lower ranking occupational positions (McGough et al., 2005). They are also at risk for social adjustment difficulties, psychological distress, higher rates of drug dependence and antisocial behavior, poor driving records with increased risk of traffic violations and accidents (Babinski, Pelham, & Molina, 2011; Langley et al., 2010; Murphy, Barkley, & Bush, 2002).

A variety of pharmacological and non-pharmacological interventions are available for the treatment of ADHD. Pharmacological interventions typically involve psychostimulants, non-stimulants, prodrug stimulants, and less commonly psychotropic medications such as antidepressants and antipsychotic medications (e.g., Dopheide & Pliszka, 2009; Faraone, 2009). Non-pharmacological interventions include a wide range including behavioral interventions, modifications to academic instruction, peer-mediated interventions, teacher-mediated programs, social skill programs, home-school communication programs, parent-training programs, time management training and anger management training to name a few (e.g., Biederman & Spencer, 2008; DuPaul & Weyandt, 2009; DuPaul, Weyandt, & Booster, 2010; DuPaul, Weyandt, & Janusis, 2011; LaForett, Murray, & Kollins, 2008; Owens et al., 2005; Pfiffner, Barkley, & DuPaul, 2006).

Studies clearly indicate that ADHD is a chronic disorder that begins early in childhood and increases an individual's risk of behavioral, social, psychological, and occupational difficulties throughout the lifespan. Given the social, economic, and interpersonal costs of the disorder, researchers have attempted to uncover the etiology of ADHD for decades. Although the precise etiology of ADHD remains unknown, genetic factors have received a great deal of attention (e.g., Williams, Tsang, Clarke, & Kohn, 2010), as have theories involving abnormalities of the dopaminergic and frontal-striatal brain systems (Sharp, McQuillin, & Gurling, 2009; Weyandt, 2006). Historically researchers inferred dysfunction of various brain regions involved in ADHD, particularly the frontal regions, based on cases of documented frontal lobe injuries that resulted in problems with attention and impulsivity (Stuss & Alexander, 2000; Weyandt & Willis, 1994). More recently, the advancement of technological methods, namely neuroimaging, has led to a surge in studies exploring the physiological substrates that may be involved in ADHD. The purpose of this article is to review a select number of neuroimaging studies, to explain their findings, to discuss the implications for understanding the physiological basis of ADHD, and to highlight methodological limitations of this body of work. Lastly, suggestions for future research are advanced.

METHOD

Relevant publications were found by searching the MEDLINE and PsycInfo databases using the keywords ADHD and the abbreviations of functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and diffusion tensor imaging (DTI). This review was restricted to these three neuroimaging techniques due to the plethora of fMRI studies and the complementary relationship between these three neuroimaging techniques. The reference lists of the articles found through the databases were then reviewed for the purpose of finding additional articles as has been done in previous reviews (Cherkasova & Hechtman, 2009). Studies that (a) appeared in peer-reviewed journals, (b) were published between 2000 and 2010, (c) used one of

these three neuroimaging techniques (i.e., fMRI, PET, and DTI), and (d) included group sample sizes of 10 or more to examine the pathophysiology of ADHD were included.

ABNORMAL BRAIN FUNCTIONING AND STRUCTURAL CONNECTIVITY IN ADHD

Results from numerous neuropsychological, pharmacological, and structural and functional brain imaging studies support that ADHD is a neurodevelopmental disorder often characterized by structural and functional brain differences compared to those without ADHD (Arnsten, 2006; Kelly, Margulies, & Castellanos, 2007; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). A variety of brain regions have been implicated in the pathophysiology of ADHD including fronto-striatal, fronto-parietal, fronto-cerebellar, fronto-striato-parieto-cerebellar, and fronto-temporal circuitry (Nigg & Casey, 2005; Rubia et al., 2009a, 2009b; Schneider et al., 2010; Silk, Vance, Rinehart, Bradshaw, & Cunnington, 2008). In addition to circuitry, specific structures and areas of the brain have also received attention and include, among others, the prefrontal cortex, anterior cingulate cortex, caudate, globus pallidus, parietal regions, temporal regions, corpus callosum, splenium, cerebellar vermis and cerebellum (Castellanos, Giedd, & Berquin, 2001; Hill et al., 2003; Konrad & Eickhoff, 2010). A discussion follows of recent neuroimaging studies that have used one of three neuroimaging techniques, namely fMRI, PET, or DTI, to examine brain functioning and structural connectivity patterns in individuals with ADHD.

ADHD and fMRI

By assessing the changes in brain metabolism (i.e., fluctuations in oxygenated versus deoxygenated blood), fMRI measures increases and decreases in regional brain activity across time (Weyandt, 2006). Specifically, fMRI allows for measurements of tissue perfusion, blood-volume changes, or changes in oxygen level concentrations. The amount of oxygenated blood delivered to specific brain areas increases following increased metabolic activity. From a measurement perspective, this increase in oxygenated blood flow is not linear to the amount of regional activity and therefore does not enable a measurement of quantitative changes in blood flow. Instead, the amount of oxygenated blood delivered to an active area typically exceeds the amount of oxygen that was actually used (Weyandt, 2006). The contrast between blood-oxygen-level—dependent is commonly referred to as BOLD (Logothetis, 2008). Unlike magnetic resonance imaging, which only provides information about brain structure, fMRI enables the examination of regional brain functioning across different contexts and cognitive demands. Therefore, according to Rubia (2002), comparing fMRI results of ADHD individuals to other clinical groups or healthy controls can lead to a better understanding of the brain functioning abnormalities associated with ADHD.

Using fMRI, a number of studies have found children and adolescents with ADHD to demonstrate hypoactivation (i.e., reduced bloodflow) in frontal regions and fronto-striatal networks compared to controls (Cubillo et al., 2010; DePue, Burgess, Willcutt, Ruzik, & Banich, 2010; Dickstein, Bannon, Castellanos, & Milham, 2006). For example, Durston and colleagues (2003) found that during a cognitive control task (Go/No-Go), 6- to 10-year-old children with ADHD demonstrated significant reductions in blood flow (i.e., “hypoactivation”) compared to controls

in the basal ganglia, ventral prefrontal cortex, and the anterior cingulate gyrus, while showing increased blood flow (i.e., “hyperactivation”) in more posterior regions of the posterior parietal lobe, posterior cingulate, and regions of the dorsolateral prefrontal cortex. These authors suggest that these hyperactivation patterns in the ADHD children may represent compensatory mechanisms in response to the impaired frontostriatal systems in children with ADHD.

Similar results have been found with adults with ADHD. For example, Valera, Faraone, Biederman, Poldrack, and Seidman (2005) used a verbal working memory task (N-back task) to assess the behavioral performance and brain activation patterns among adults with and without ADHD. Results indicated that adults with ADHD demonstrated decreased activation in the left inferior occipital and cerebellar regions, and a “trend of deactivation” in an area of the right prefrontal cortex, possibly suggesting underactivation in fronto-cerebellar circuitry. These findings are supportive of Rubia et al. (2009a, 2009b) who found reduced fronto-striato-parieto-cerebellar activation in medication naïve children with ADHD during a rewarded continuous performance task. Particularly noteworthy about this study is that administration of a single dose of methylphenidate, increased activation throughout this same network, suggesting methylphenidate may help regulate or “normalize” fronto-striato-parieto-cerebellar functioning.

Recently some researchers (Kobel et al., 2010; Silk et al., 2005) have suggested that the parietal and temporal regions may play an important role in ADHD due to anatomical studies that have found reduced total brain volumes and reduced volumes in these areas (Carmona et al., 2005; Castellanos et al., 2002). Vance et al. (2007) found evidence for a right striatal parietal dysfunction in ADHD boys. Specifically, while performing a spatial working memory task, boys with ADHD were found to have decreased activation in the cuneus, precuneus, and the right inferior parietal lobe compared to a control group of age and IQ-matched boys. Similarly, Schneider and colleagues (2010) found hypoactivation in fronto-striatal and parietal attention systems in adults with ADHD compared to controls during No-Go task conditions of a Go/No-Go task. Furthermore, in this same study (Schneider et al., 2010) increased levels of deactivation in the parietal lobule, as well as the anterior cingulate cortex (ACC) and parietal cortical structures, were significantly negatively correlated with ADHD symptom severity. The findings from this study suggest that symptom severity is associated with level of fronto-striatal and parietal dysfunction in ADHD. Additionally, using a recently developed meta-analytic approach known as activation likelihood estimation, Dickstein and colleagues (2006) examined 13 fMRI studies (and three PET studies) and found summative evidence for fronto-striatal and fronto-parietal hypofunctioning in individuals with ADHD compared to controls.

Along these same lines, Rubia, Smith, Brammer, and Taylor (2007) found medication-naïve boys with ADHD had reduced activation in the bilateral superior temporal lobes, basal ganglia, and posterior cingulate during a visual oddball task compared to a control group of handedness and IQ-matched boys. Smith, Taylor, Brammer, Toone, and Rubia (2006) showed that during a cognitive flexibility task, medication naïve boys with ADHD demonstrated hypoactivation in the bilateral prefrontal cortex and temporal lobes and right parietal lobe compared to age, gender, and IQ-matched healthy controls. Boys with ADHD also demonstrated impaired performance on this task by demonstrating slower and more variable response times.

An advantage of fMRI is that it enables researchers to examine temporally correlated brain activity across proximal and distal brain regions, thus permitting inferences regarding the functional connectivity of different anatomical regions (Konrad & Eickhoff, 2010). Therefore, instead of simply examining hyper- and hypofunctioning of specific brain regions, fMRI studies have

recently been used to examine differences in the functional connectivity of brain regions between individuals with ADHD and controls (Cubillo et al., 2010; Konrad & Eickhoff, 2010). Function connectivity is defined as “the temporal correlation or coherence of spatially remote neuropsychological events” (Konrad & Eickhoff, 2010, p. 905). Functional connectivity studies have found evidence of significantly lower connectivity in fronto-parietal and fronto-striato-parieto-cerebellar networks in adolescents and adults with ADHD compared to controls (Rubia et al., 2009a, 2009b; Wolf et al., 2009), which is consistent with the previously discussed studies showing hypoactivation throughout these same networks.

Abnormal activation and connectivity within the “default mode network” (DMN) has also been found in children with ADHD (Fassbender, 2009). The DMN refers to the brain circuitry that includes the medial prefrontal cortex, posterior cingulate, precuneus, and the medial, lateral, and inferior parietal cortices. This network is believed to be associated with task irrelevant mental processes and mind wandering (Fassbender, 2009; Schilbach, Eickhoff, Rotarska-Jagiela, Gereon, & Vogeley, 2008). According to Sonuga-Barke and Castellanos (2007) some individuals with ADHD have difficulty effectively suppressing the DMN during task related mental processes, which leads to lapses in attention and inconsistent behavioral responding. Indeed, functional connectivity studies have found that ADHD is associated with an “under connectivity” within this network compared to controls (Cao, 2006; Castellanos, Margulies, & Kelly, 2008). Furthermore, Peterson et al. (2009) showed that a group of children and adolescents with ADHD were unable to suppress DMN activity to the same degree as controls while performing the Stroop Color and Word Test. After methylphenidate administration, however, DMN activity in the ADHD group was comparable to that of controls. This finding suggests that methylphenidate enabled effective suppression of DMN activity in the children and adolescents with ADHD.

As mentioned previously, a limited number of fMRI studies have shown that methylphenidate and other stimulant medications tend to “normalize” brain activation patterns and functional connectivity in individuals with ADHD, within both the DMN and the previously discussed regions associated with fronto-striato-parieto-cerebellar circuitry (Peterson et al., 2009; Rubia et al., 2009a, 2009b). Additional fMRI studies are still needed to further clarify the specific regions that demonstrate increased or improved functioning after administration of different dosages of stimulant medications.

ADHD and PET

PET is a functional neuroimaging technique that involves the intravenous injection of radioactive compounds (which consist of radioactive isotopes binded with glucose or oxygen) into the bloodstream. These radioactive compounds eventually pass the blood–brain barrier and shed positively charged particles that collide with electrons creating photons, which can be traced by a PET scanner (Weyandt, 2006; Zimmer, 2009). Although not part of the current review, previous PET studies have examined glucose and PET provides a general measurement of functional activity via glucose metabolism and blood flow metabolism and a number of studies have been published regarding PET and ADHD (Lou, Henriksen, & Bruhn, 1984). PET also enables more specific analyses of neurotransmitter binding site density through the use of specific neuroreceptor radiotracers. This method provides more detailed information regarding presynaptic, postsynaptic, and transporter binding of different neurotransmitters throughout diverse brain regions and networks

(Zimmer, 2009). In fact, although PET is able to compare changes in metabolic brain activity of ADHD groups to other clinical groups and controls (Ernst et al., 2003), the majority of recent PET studies using ADHD samples have focused on examining differences and changes in neurotransmitter binding and receptor density (Zimmer, 2009).

Due to the effectiveness of stimulant medication in treating many individuals with ADHD and that stimulants appear to primarily influence dopaminergic systems (Volkow, Wang, Fowler, & Ding, 2005), some authors have suggested that ADHD is characterized by catecholamine deficits, particularly dopamine and neuroepinephrine (Arnsten, Berridge, & McCracken, 2009; Tripp & Wickens, 2009). Supporting this hypothesis are a number of PET studies that have found abnormal dopamine transporter (DAT) binding, dopamine receptor binding, and dopamine metabolism in adolescents and adults with ADHD (Jucaite, Fernell, Halldin, Forsberg, & Farde, 2005; Ludolph et al., 2008; Spencer et al., 2005). It should be noted that dopamine transporter or receptor *density* is believed to reflect transporter or receptor binding since an increased number or density of transporters and receptors should likely reflect increased binding potential. Compromised levels of dopamine transporter density and binding are believed to negatively impact the functioning of dopaminergic systems. Spencer and colleagues (2007), for example, found increased DAT binding in the right caudate of an adult group of non-comorbid treatment naïve ADHD participants compared to a matched control group that was characterized by a low number ADHD symptoms. Increased DAT density is not a robust finding, however, as others such as Jucaite et al. (2005) failed to find increased DAT density in the striatum in an ADHD group. Decreased DAT density was found in the midbrain of the ADHD sample compared to the control sample, however.

In addition to studies exploring DAT density and binding, Volkow, Wang, and Newcorn (2007), examined postsynaptic dopamine receptor availability and found that a group of 19 medication-naïve adults with ADHD showed decreased D₂/D₃ receptor availability in the left caudate compared to 24 healthy controls. Furthermore, following administration of methylphenidate, the ADHD group demonstrated decreased dopamine activity in the caudate compared with controls. This decreased response in the ADHD group was also significantly correlated with inattentive symptoms, suggesting a relationship between dopaminergic activity and symptoms of inattention.

Although neuroepinephrine, serotonin, and other neurotransmitter systems (e.g., cholinergic system) have been implicated in the pathophysiology of ADHD (Arnsten et al., 2009), to date, no clinical studies using PET have been used to assess the functioning of these systems within an ADHD sample (Zimmer, 2009). Therefore, PET studies examining receptor binding and density of these and other neurotransmitter systems in children, adolescents, and adults with ADHD are sorely needed.

ADHD and DTI

Diffusion tensor imaging is a neuroimaging technique (Konrad & Eickhoff, 2010; Le Bihan, 2003) that has only recently been used to study structural white matter in individuals with ADHD. Unlike fMRI and PET, which are both functional neuroimaging techniques, diffusion tensor imaging provides an assessment of the axonal organization of the brain by measuring the translational motion of water molecules, thus enabling inferences regarding the structural connectivity of brain anatomy and potential axonal injury (Mori & Zhang, 2006). Most studies using DTI to examine

the structural connectivity patterns associated with ADHD have compared functional anisotropy (FA) values of specific brain regions of ADHD samples to controls. Fractional anisotropy is a commonly used index based on DTI, with higher FA values indicating either a decrease in regional axonal branching or an increase in axonal bundle density or myelination (Mori & Zhang, 2006).

Although DTI has been used to explore macro and microstructural attributes of brain regions such as the corpus callosum in children with a variety of disorders including reading disorders (e.g., Hasan et al., 2012), only a handful of studies have used DTI to measure brain region structural connectivity in children and adults with ADHD (Ashtari et al., 2005; Cao et al., 2010; Casey et al., 2007; Silk, Vance, Rinehart, Bradshaw, & Cunnington, 2009). Most of these studies have reported white matter “abnormalities” in participants with ADHD. For example, Konrad et al. (2010) found elevated FA in the white matter structures of the bilateral temporal lobe, while reduced FA was found in the orbitomedial prefrontal white matter and in the right anterior cingulate bundle in medication-naïve adults with ADHD compared to controls. The authors interpreted the findings from this study as demonstrating a lack of white matter integrity in the fronto-striatal circuitry of ADHD patients. In a comparison study between children with ADHD and age and gender-matched controls, Ashtari and colleagues (2005) found decreased FA in the right premotor, right striatal, right cerebral peduncle, left middle cerebellar peduncle, left cerebellum, and left parieto-occipital areas in the ADHD children, also suggesting white matter “abnormalities” in fronto-striatal as well as fronto-cerebellar circuitry. Alternatively, Silk et al. (2009) found increased FA in inferior parietal, occipito-parietal, inferior frontal, and inferior temporal cortex in children and adolescents with ADHD compared to controls.

Makris and colleagues (2008) reported that, compared to controls, adults with ADHD demonstrated white matter abnormalities in pathways subserving executive functioning and attentional networks. Specifically, significantly smaller FA values in the cingulum bundle and superior longitudinal fascicle II were found relative to a control region (fornix), thus demonstrating white matter structural abnormalities in adult ADHD. These findings are similar to another study that also found reduced FA in the superior longitudinal fascicle II in ADHD patients compared to age-matched controls (Hamilton et al., 2008).

Pavuluri and colleagues (2009) found lower FA in the anterior corona radiata of children and adolescents with ADHD compared to controls. These authors also found decreased FA in the anterior limb of the internal capsule and the superior region of the internal capsule of children and adolescents with ADHD compared to children and adolescents diagnosed with pediatric bipolar disorder and controls. This is one of two studies using DTI to demonstrate differential structural connectivity patterns in an ADHD sample compared to another clinical group. The other study (Davenport, Karatekin, White, & Lim, 2010) compared FA in adolescents with ADHD to adolescents with schizophrenia and controls and found significantly elevated FA in left superior and right inferior frontal regions for the ADHD group compared to the other two groups. The group with schizophrenia and the group with ADHD both showed lower FA in the left posterior fornix. Furthermore, adolescents with Schizophrenia had lower FA in bilateral cerebral peduncles, anterior and posterior corpus callosum, right anterior corona radiata, and right superior longitudinal fasciculus compared to the other two groups. This last finding is particularly interesting due to its inconsistency with the previously mentioned studies that found ADHD to be associated with decreased FA in the anterior corona radiata (Pavuluri et al., 2009) and superior longitudinal fascicle (Hamilton et al., 2008; Makris et al., 2008). As previously mentioned, FA

values may indicate either a decrease in regional axonal branching or an increase in axonal bundle density or myelination (Mori & Zhang, 2006). Therefore, although most DTI studies have found abnormal structural anatomical connectivity in children, adolescents, and adults with ADHD, it is difficult to determine whether or not this abnormality represents deficient axonal branching or deficient myelination, hence the results from these DTI studies are difficult to interpret (Konrad & Eickhoff, 2010; Silk et al., 2009).

Methodological Concerns

It is indisputable that brain imaging techniques including fMRI, PET, and DTI have contributed to our understanding of brain functioning and have fueled an eruption of studies in cognitive neuroscience. Indeed, these methods have led to the promulgation of theories and hypotheses concerning the physiological basis of ADHD and have contributed to a better understanding of brain regions and substrates that may be involved in ADHD. These technologies are not without limitations, however, and findings can be easily misconstrued if these limitations are unrecognized. For example, there is a misperception that fMRI and PET reflect blood flow or metabolism changes in real time when in fact there can be a several second delay between the time of the change in activity and the recording. For example, fMRI assesses the level of oxygenated to deoxygenated blood near the area of increased neuronal activity—which is presumed to be the result of increased cognitive demand in that area. The amount of blood that is delivered to an active area however does not necessarily follow a linear relationship and instead the amount delivered typically exceeds that which is needed. This process can take up to several seconds and consequently fMRI is not measuring quantitative changes in blood flow or metabolism but instead indirectly assesses changes in these indices (Papanicolaou, 1998). This principle applies to PET as well which can be further complicated by the delay between the time of the injection of the radioactive isotope/tracer and the uptake by the tissue of interest (Bailey, Townsend, Valk, & Maisey, 2005). FMRI signals also can be misleading, as Logothetis (2008) aptly noted, when areas of the brain are inhibited (i.e., decreased neuronal firing) as they too, are characterized by increased metabolic demands. A serious methodological limitation concerns procedures followed when obtaining PET scans. Currently, neuroimaging procedures are not uniform or standardized from one study to another and therefore variation exists in the type of mathematical algorithms chosen, signal thresholds, ordinates, contrasts, colors, and statistical procedures employed to analyze the data (Reeves, Mills, Billick, & Brodie, 2003).

Interpretation of neuroimages is also problematic when trying to make inferences regarding clinical populations as most studies focus on change or difference in activity, however there is a dearth of information concerning baseline activity of the “normal” brain let alone the “clinical” brain. Gusnard, Raichle, and Raichle (2001), for example, suggested that while at rest the brain likely involves consistent activity in some brain regions and less in others, and it is highly probable that factors such as genetics, age, sex, health, and emotional states affect baseline brain activity. This principle applies to DTI as well, since there is also a lack of information regarding “normal” white matter patterns in children, adolescents, and adults. Furthermore, it is critical to note that anatomical differences between individuals with and without ADHD do not necessarily relate to behavioral differences. For example, although several DTI studies have found

either a decrease in regional axonal branching or an increase in axonal bundle density or myelination in individuals with ADHD relative to control subjects, this finding does not necessarily relate to the behavioral symptoms characteristic of the disorder and warrants empirical investigation. The same issue applies to receptor density studies. Given this issue, it would behoove us in the scientific community to avoid describing findings as “abnormal” (i.e., abnormal blood flow, abnormal circuitry, abnormal connectivity, abnormal activation) and instead to use more accurate descriptive terms such as “statistically less activity” or “statistically less glucose metabolism” or “different” when comparing neuroimaging findings between participants with ADHD and control subjects. Ultimately, in order for neuroimaging findings to be clinically meaningful, additional studies are needed that demonstrate (a) consistency in findings across studies, (b) the anatomical and/or functional differences correlate with behavioral differences, (c) the findings are unique to ADHD (and not simply characteristic of pathology), and that the anatomical and functional findings are not present in those without behavioral symptoms, (d) the findings are reliable and present longitudinally, (e) functional changes follow the administration of a treatment and results in diminishment of behavioral symptoms. Only the latter has been found with medication studies and there are inconsistencies across these studies as well (Peterson et al., 2009; Rubia et al., 2009a, 2009b).

A related methodological concern pertains to the reliability of the images. Nearly all neuroimaging ADHD studies are cross-sectional in nature and the scans are taken at one point in time. In other words, it is unknown whether the same findings (hyper/hypoperfusion, increased/decreased glucose metabolism, white matter differences) would be found one hour later, one day later, or one year following the original scan. Replication studies are sorely needed as are longitudinal studies with the ADHD population. Indeed, replication studies would help to address the problematic issue of inconsistent findings across studies. For example, although a number of fMRI studies have supported decreased activity in the frontal regions of individuals with ADHD, other studies have found increased activity or no difference relative to control groups (Durstun et al., 2003; Vance et al., 2007). Similarly, PET and DTI studies have also produced inconsistent findings with respect to receptor density and white matter integrity (Davenport et al., 2010; Hamilton et al., 2008; Jucaite et al., 2005).

Most of the studies are limited in their generalizability due to a number of methodological problems. For example, small samples (20 or less) are typical for studies involving ADHD participants yet the number of statistical analyses performed is substantial, often multivariate in nature, leading to an increased risk of Type I error rate. Similarly, effect sizes are often not reported and those that are tend to be small, thereby compromising the statistical power of the designs. Other potential confounding factors that are rarely discussed in studies include intelligence and ethnicity. Studies are also methodologically hampered by restricted age range, comorbidity, and a lack of representation of ADHD subtypes.

As mentioned previously, interpretation of neuroimaging findings can be affected by a number of technological factors and can also be misinterpreted as causal findings. For example, a number of studies have reported hypoperfusion of the frontal lobe regions in individuals with ADHD compared to control subjects, and this can easily be misconstrued as evidence that the reduction in blood flow is causing the ADHD-related symptoms. Neuroimaging studies are purely correlational, in nature, however, and *do not reveal what is causing* the reduction in blood flow. A related and critical point is that many of the neuroimaging findings are not unique to ADHD and have been found in a vast array of clinical disorders. For example, hypoperfusion of the frontal lobes

has been found in patients with schizophrenia, Parkinson's disease, Alzheimer's disease, depression, and others and is not diagnostic of ADHD (Grimm et al., 2008; Kaataoka et al., 2010; Lotze et al., 2009; Pihlajamaki et al., 2010; Takahashi, Ishii, Shimada, Ohkawa, & Nishimura, 2010; Wake et al., 2010).

CONCLUSION

In summary, fMRI, PET, and DTI studies are often interpreted as evidence that ADHD is a result of abnormal anatomical functioning and connectivity throughout fronto-striatal, fronto-temporal, fronto-parietal, and/or fronto-striato-parieto-cerebellar circuitry. Although many of these studies support hypofunctioning or compromised white matter integrity within these networks, results have been inconsistent and some studies have found increased rather than decreased regional brain activation, especially throughout the DMN. Each of these neuroimaging techniques provides unique information regarding the pathophysiology of ADHD, but they also are characterized by unique methodological limitations (Rubia, 2002; Zimmer, 2009). Both fMRI and PET, for example, are indirect measures of brain activity and do not immediately assess neuronal brain activity. None of the techniques reveal causal factors pertaining to the physiological underpinnings of ADHD; rather, the studies are relational in nature. Although a pattern can be discerned in the literature implicating the frontal-striatal regions (as well as others) in ADHD, there are substantial inconsistencies in findings across the studies. Methodological limitations likely contribute to these inconsistencies and include issues such as a lack of standardized procedures for designing, conducting, analyzing, and interpreting the scans, technological differences in equipment, small sample sizes, inappropriate statistical analyses leading to inflated Type I error rates and compromised statistical power, and a host of subject variables. Ideally, future studies should refrain from referring to findings as abnormal and instead rely on more accurate descriptive terminology, increase sample sizes and statistical power perhaps by conducting more multi-site investigations, standardize scanning procedures and interpretations guidelines, address comorbidity issues, and other subject variables, and replicate when possible. Although neuroimaging techniques are useful in research and aid in exploring the pathophysiology of ADHD, these technologies currently lack adequate specificity and sensitivity for psychiatric conditions and therefore should not be used for informing clinical practice. Lastly, future research should focus on addressing the methodological limitations discussed herein and attempt to integrate findings across anatomical, behavioral, and neuroimaging techniques to better elucidate the physiological underpinnings of ADHD.

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