

Brain structure differences in ADHD patients: A VBM meta-analysis

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is estimated to affect 8-12% of the populace. ADHD is divided into subtypes and is defined by a variety of hyperactive and/or inattentive symptoms. As a developmental disorder, ADHD is suspected of being a product of abnormal brain structure and function. Numerous imaging studies have been published that have identified a variety of brain abnormalities that correlate with ADHD. The purpose of the current project was to run a meta-analysis on neuroimaging studies in order to identify brain abnormalities that commonly correlate with ADHD across several studies. Articles for the meta-analysis were identified through a PubMed search. Out of an initial 274 articles, seven fit the criteria for inclusion in the meta-analysis: three voxel-based morphometry (VBM) studies to assess grey matter findings, three fractional anisotropy (FA) studies to assess white matter findings, and one study that used both measurements. Meta-analysis was performed with Signed Differential Mapping (SDM) software. White matter differences were identified in the prefrontal cortex, the anterior temporal lobes, and several areas of the occipital lobes. Grey matter differences were identified in the inferior prefrontal cortex, the medial frontal lobes, the dorsal frontal lobes, the dorsal parietal lobes, the inferior temporal lobes, and the anterior cerebellum.

Brain structure differences in ADHD patients: A VBM meta-analysis

Attention-deficit/hyperactivity disorder (ADHD) is a developmental disorder that is typically diagnosed in childhood and has an estimated prevalence of 8-12%, with males outnumbering females 3 to 1 (Valera, Stephen, Murray, & Seidman, 2007) and with most cases continuing into adulthood (American Psychiatric Association [*DSM-IV-TR*], 2000). ADHD is divided into three generally accepted subtypes: predominantly inattentive, predominantly hyperactive, and combined (Purper-Ouakil, Ramoz, Lepagnol-Bestel, Gorwood, & Simonneau, 2011). It has been argued, however, that the inattentive subtype qualifies as its own distinct disorder (Carmona, et al., 2005). Symptoms are categorized as either inattentive or hyperactive, with inattentive symptoms including daydreaming, distractibility, and difficulty focusing on tasks, while hyperactive symptoms include restlessness, excessive talking, and impulsivity. While some level of the preceding traits are typical of certain age groups, the keystone of ADHD diagnosis is that all observed symptoms are inconsistent with developmental level (Purper-Ouakil, Ramoz, Lepagnol-Bestel, Gorwood, & Simonneau, 2011). The most common and problematic results of ADHD pathology are accidents and injury, strain on relationships, and inappropriate behavior. ADHD symptoms also change predictably as time passes, with hyperactive symptoms typically decreasing through adolescence and eventually stabilizing at normal or near-normal levels by early adulthood, and inattentiveness and impulsivity lasting throughout the life span (Konrad, et al., 2010; Biederman, 2005).

Treatment can be difficult, as ADHD often manifests comorbidly with other pathologies (Yang, Wang, Chuang, Jong, Chao, & Wu, 2008; van 't Ent, et al., 2007), the most common of which are Tourette's syndrome, drug and alcohol abuse, depression, and a variety of learning disorders (Purper-Ouakil, Ramoz, Lepagnol-Bestel, Gorwood, & Simonneau, 2011). The most

common treatment for ADHD is medication with stimulants such as methylphenidate and dextroamphetamine, though some non-stimulant drugs, like atomoxetine, have also proven effective (Curatolo, D'Agati, & Moavero, 2010). There has been evidence that extensive behavioral therapy can be effective, as well (Curatolo, D'Agati, & Moavero, 2010).

In addition to the previously listed symptoms, research has revealed secondary criteria that may be used to help confirm an ADHD diagnosis. Delayed maturation in early childhood, for example, such as late sitting up and rolling over, often correlates with a diagnosis of ADHD later in life (van 't Ent, et al., 2007). Several cognitive deficits have also been suggested as endophenotypes of ADHD risk, such as difficulties with response inhibition and delay aversion (Aron & Poldrack, 2005; Purper-Ouakil, Ramoz, Lepagnol-Bestel, Gorwood, & Simonneau, 2011). The possible use of such endophenotypes in diagnosing or confirming ADHD would be particularly useful with older patients, as cognitive problems (e.g. distractibility) tend to continue through the life course, while behavioral problems (e.g. restlessness) diminish (Purper-Ouakil, Ramoz, Lepagnol-Bestel, Gorwood, & Simonneau, 2011).

While still not advanced enough to assist with diagnoses, improvements in brain imaging technologies have been instrumental in revealing a number of structural and/or functional brain abnormalities that correlate with ADHD. Most of these advances have occurred within the last 10 years, as brain scanning technologies before that time were fraught with both technical (e.g. poor spatial resolution) and ethical (e.g. using radioactive substances on healthy controls) difficulties, which in turn led to low sample sizes and inconsistent/contradictory results (Giedd, Blumenthal, Molloy, & Castellanos, 2001). Historically, post-mortem brain analyses were also possible, but such research was intrinsically confounded by self-selection (brains have to be donated) and by possible causes of death, as things like car crashes or drowning can lead to

widespread brain tissue malformations. Post-mortems also cannot provide insight into function. Even with the advent of reliable and detailed imaging technologies, methodological differences between projects often lead to incompatible or contradictory results, making the identification of common abnormalities difficult.

Despite methodological disagreements, modern imaging and DNA analysis techniques have provided neural and genetic insight into the physiological bases of ADHD. Recent findings regarding common alleles, neurotransmitter abnormalities, and structural differences in areas such as the frontal lobes and cerebellum have begun to reveal possible pathway dysfunctions that lead to ADHD symptoms. Overall brain matter (both grey and white) volume, for example, is typically reduced in ADHD patients relative to controls and functional imaging analyses consistently show activation differences between ADHD patients and controls (Aron & Poldrack, 2005), though different studies have reported opposite findings (i.e. greater/lesser activation than controls), possibly indicating different ADHD subtypes. These activation differences have been shown to normalize under the administration of certain drugs, supporting their widespread use in treatment (Biederman & Spencer, 1999; Aron & Poldrack, 2005). ADHD symptoms, or symptoms similar enough to qualify for an ADHD diagnosis, may also result from problems in completely different parts of the brain. The prefrontal cortex, for example, has been implicated in a large number of ADHD cases, as abnormalities in this area are associated with the problematic regulation of attention (i.e. attending to something of high salience like a comic book, but not to something of low- or non-salience like a school lecture). Abnormalities in the parietal association areas, however, can also negatively affect attention, only in this case by directly hampering any ability to attend at all (i.e. difficulty attending to either salient or non-salient stimuli). This implies that various ADHD diagnoses may in fact be the result of different

brain problems in different patients (Arnsten, 2009), which in turn may explain both the apparent contradictions often seen between various imaging studies and the fact that ADHD patients often differ in their reactions to medication.

Potential Causes: Genes and Environment

Most of the research on the potential causes of ADHD has indicated strong genetic influences in the disorder. Twin studies, for example, have produced heritability scores for ADHD of approximately 0.76 for children and adolescents and 0.30 for adults (Purper-Ouakil, Ramoz, Lepagnol-Bestel, Gorwood, & Simonneau, 2011). Genes for dopamine regulation, such as the dopamine D4 receptor (DRD4) gene, are the strongest candidates for genetic causes of ADHD (Biederman & Spencer, 1999); a 7-repeat version of this gene, which is more common in ADHD patients than in the wider populace, has been postulated to inhibit GABA-ergic interneurons, which in turn diminishes activity in prefrontal pyramidal cells (Arnsten, 2009), possibly leading to the activation deficits seen in many ADHD patients during attention tasks. Individuals with a 10-repeat allele of dopamine transporter gene (DAT1) have been shown both to make more errors in response inhibition tests than individuals with the more common 9-repeat allele, and to respond differently to methylphenidate treatment (Aron & Poldrack, 2005), specifically showing decreased arousal in the prefrontal cortex after treatment. DRD4 and DAT1 expression have also been correlated with volume differences in the prefrontal cortex and caudate nucleus, respectively (Purper-Ouakil, Ramoz, Lepagnol-Bestel, Gorwood, & Simonneau, 2011). Other neurotransmitter genes have also been implicated in ADHD. Two copies of Taq 1, a polymorphism for the gene that codes for the enzyme dopamine beta hydroxylase (which synthesizes norepinephrine), are more common in ADHD patients (Arnsten, 2009), as are certain

polymorphisms for the gene for the serotonin receptor 5-HT_{1B} (Aron & Poldrack, 2005). Genetic issues can be difficult to parse, however, as different genetic effects may result in similar, or effectively identical, phenotypic effects. One gene variation, for example, may result in lowered production of dopamine in certain prefrontal circuits, while variation in a different gene may lower the number of postsynaptic dopamine receptors in the same circuits; two separate ADHD patients, each with one of the aforementioned variations, would present with essentially identical symptoms, yet divergent genotypes. This, in turn, can lead to the conclusion that neither patient's symptoms are genetically mediated.

As for potential environmental causes, research has indicated that influences occur pre- or perinatally and are largely biological or biochemical in nature (Curatolo, D'Agati, & Moavero, 2010). Physiological stressors, such as low birth weight or brief hypoxia, strongly predict later ADHD diagnosis (van 't Ent, et al., 2007), as do maternal smoking and drinking habits during pregnancy (Curatolo, D'Agati, & Moavero, 2010). Most work in the area of environmental influences on ADHD has indicated that stressors, particularly in early life, are major components of ADHD development only in genetically predisposed individuals. One study, for instance, performed on children conceived via *in vitro* fertilization, demonstrated that prenatal stress was linked to the development of ADHD only when the nascent child and mother were related to each other; similarly, one twin study showed that genetic factors play an increased role in symptom development in the context of high environmental stress (Purper-Ouakil, Ramoz, Lepagnol-Bestel, Gorwood, & Simonneau, 2011).

Catecholamine Pathways

As indicated by genetic findings, a great deal of evidence implicates catecholamine abnormalities in most, if not all, cases of ADHD. The brain areas that are primarily associated with one of these neurotransmitters, dopamine, are the basal ganglia, a collection of sub-neocortical structures that connect to numerous brain areas and are involved in a wide variety of activities. Of particular relevance to ADHD pathology are the basal ganglia's involvement in voluntary motor control, procedural learning, and, in concert with frontal lobe input, the selection of actions from a list of possible choices (Gazzaniga, Ivry, & Mangun, 2009). The occurrences of ADHD symptoms after basal ganglia strokes or trauma, particularly those involving the putamen, present evidence for the influence of dopaminergic pathway abnormalities in ADHD pathology (van 't Ent, et al., 2007), as do regularly observed structural deficits in the caudate, putamen, and pallidum (all portions of the basal ganglia) in ADHD patients (Aron & Poldrack, 2005). Some research has shown that structural deficits in the right caudate body are strongly negatively correlated with the severity of ADHD symptoms in children with combined-type ADHD (Soliva, et al., 2010), demonstrating the potential utility of brain imaging techniques in the early diagnosis of ADHD. When given methylphenidate, caudate and putamen activity increases in ADHD patients, yet decreases in controls (Giedd, Blumenthal, Molloy, & Castellanos, 2001), though it is important to note that the said ADHD patients had been previously treated while the controls were drug-naïve. More generally, stimulants act primarily on the D1 receptors in the prefrontal cortex, which is vital for attention and decision-making, and the D2 receptors in the striatum, which is the largest portion of the basal ganglia (Purper-Ouakil, Ramoz, Lepagnol-Bestel, Gorwood, & Simonneau, 2011). Norepinephrine and serotonin imbalances have also been implicated in ADHD pathology, though

the involvement of these two neurotransmitters appears to have been deduced largely through *post hoc* observation of behavioral changes after treatment with medication. Certain non-stimulants, for example, such as atomoxetine and guanfacine, have been shown to improve ADHD symptoms and are known to increase norepinephrine, and in some cases dopamine, levels preferentially in the prefrontal cortex by way of reuptake inhibition (Purper-Ouakil, Ramoz, Lepagnol-Bestel, Gorwood, & Simonneau, 2011). Similarly, monoamine oxidase inhibitors (MAOIs), which maintain high levels of serotonin in the synaptic cleft by deactivating the enzymes that break it down, have also been shown to be effective in some ADHD patients (Curatolo, D'Agati, & Moavero, 2010).

Frontal Cortex Areas

First and foremost of the “higher” brain structures implicated in ADHD pathology are those of the prefrontal cortex, especially on the right side. Specifically, the dorsomedial area of the right hemisphere has been implicated in planning and committed decision-making (Damasio, 2005) and the inferior ventrolateral area has been implicated in response inhibition (Aron & Poldrack, 2005). Both structural and functional abnormalities in these brain areas correlate with ADHD pathology.

The right prefrontal cortex, which receives numerous axonal inputs from the basal ganglia, can only perform its duties in maintaining concentration and resisting distraction when the neurochemical environment is properly balanced, hence the correlation between norepinephrine and/or dopamine imbalance and ADHD symptoms (Arnsten, 2009). Specifically, norepinephrine increases appropriate prefrontal connections by way of receptor up-regulation and dendritic branching, while dopamine decreases inappropriate connections through largely

analogous mechanisms (Arnsten, 2009). Research on adult cases of ADHD has found severe volume reduction in the left orbitofrontal cortex (Konrad, et al., 2010), indicating that problems with sensory integration may be responsible for, or may at least compound, issues of distractability and poor attention. The role of frontal lobe abnormalities in ADHD has been supported by fMRI research that has shown delayed frontal lobe activation during tasks involving attention, response inhibition, decision making, and working memory (Aron & Poldrack, 2005; Wang, Jiang, Cao, & Wang, 2007).

Cerebellum

Long viewed purely as the brain's coordination center, the cerebellum has lately become an area of strong neurological interest. Recent research has indicated notable cerebellar involvement in systems and states as varied as language, affect, attention, social interaction, learning, and memory (Tiemeier, Lenroot, Deanna, Tran, Pierson, & Giedd, 2010; Yang, Kim, Kim, Kim, Kwak, & Han, 2009). This breadth of involvement is hardly surprising considering that the cerebellum, which comprises approximately 15% of the brain's overall mass, contains over half of all the brain's neurons, and is connected to several brain areas that are associated with numerous behaviors, such as the prefrontal cortex. The cerebellar vermis has an important role in the regulation of the substantia nigra (Yang, Kim, Kim, Kim, Kwak, & Han, 2009), indicating that cerebellar dysfunction may be directly related to the catecholaminic imbalances observed in ADHD cases. The cerebellar vermis also has more glucocorticoid receptors than any other brain region, including the hippocampus (Yang, Kim, Kim, Kim, Kwak, & Han, 2009), suggesting a role for stress in the development ADHD pathology. Stress-sensitivity in the cerebellum may be the source of the positive correlation between childhood distress and ADHD

diagnosis observed by van't Ent et al. (2007). A cerebellar-thalamic-prefrontal circuit has also been postulated by some researchers to be a major pathway for attention regulation, and this pathway may also be dysfunctional in some cases of ADHD (Giedd, Blumenthal, Molloy, & Castellanos, 2001).

Other Findings

Right hemisphere frontal-striatal-parietal-temporal networks are known to be heavily involved with executive functioning, and damage to or malformation of these pathways is suspected to be a major contributor to ADHD pathology (Konrad, et al., 2010; Carmona, et al., 2005). The right temporal lobe has also been implicated in ADHD pathology, as grey matter reductions in the right medial temporal area are associated with impulsivity and distractibility (Kobel, et al., 2010). No difference has been found between overall grey matter and white matter volumes between subtypes (Carmona, et al., 2005), though it is possible that the experimental subgroups were not large enough to provide for powerful analysis of between group differences. The anterior corpus callosum shows reduced volume in ADHD adolescents, and a reduction in the posterior corpus callosum has been noted in stimulant non-reactive ADHD patients (Giedd, Blumenthal, Molloy, & Castellanos, 2001), indicating that such a structural abnormality may indicate either comorbid learning disabilities or a unique ADHD subtype.

Some evidence has indicated that brain structure abnormalities are different between ADHD cases determined to have a predominantly genetic risk and those with a predominantly environmental risk (van 't Ent, et al., 2007). According to one study—performed with both monozygotic and dizygotic twins, raised both together and apart—genetic risk correlates with white matter volume reduction in both orbitofrontal areas and the posterior corpus collosum,

while environmental risk correlates with white matter volume reduction in the inferior dorsolateral prefrontal cortex (van 't Ent, et al., 2007). Some structural differences have also been seen between the sexes, with ADHD females showing more gray-matter volume reduction in the posterior cingulum and the right precuneus than ADHD males (Yang, Wang, Chuang, Jong, Chao, & Wu, 2008). Females have also been found to have volume reduction in the posterior-inferior lobules of the cerebellar vermis (Castellanos, Giedd, Berquin, Walter, Sharp, & Tran, 2001). Since cerebellar development is known to be strongly sexually dimorphic (Tiemeier, Lenroot, Deanna, Tran, Pierson, & Giedd, 2010), specifically developing faster in normal females compared to normal males, the smaller size in ADHD females may indicate a distinct pathway for ADHD symptom expression in females. Sex-related structural differences also correlate with different diagnostic criteria; Almeida Montes et al. (2010) found that in males grey matter volume reduction in the right caudate correlated strongly with DSM-IV-TR criteria for hyperactivity, impulsivity, and inattention, while females showed a strong correlation between the same volume reduction and DSM-IV-TR criteria for impulsivity, but not inattention or hyperactivity. Sex differences have also been seen in brain function, as in one study that showed increased occipital consumption of glucose in males but not females (Wang, Jiang, Cao, & Wang, 2007), though the implications of the finding are not clear.

Overall grey matter reduction has also been reported (Yang, Wang, Chuang, Jong, Chao, & Wu, 2008; Carmona, et al., 2005), particularly in the cerebellum (Castellanos, Giedd, Berquin, Walter, Sharp, & Tran, 2001) and the temporal lobes (Wang, Jiang, Cao, & Wang, 2007), and white matter volume has been consistently reported as being 4-6% lower than in healthy controls (Ashtari, et al., 2005). Left hippocampus-amygdala volume reductions have also been noted, though such abnormalities may be a sign of more general pathology or developmental lag, as

similar reductions are seen in schizophrenia, bipolar disorders, and autism spectrum disorders (Brieber, et al., 2007). Volume increases have also been observed, such as in right occipital lobe and the left posterior lateral ventricle (Wang, Jiang, Cao, & Wang, 2007), though the latter finding is likely due to reductions in surrounding brain tissue.

Fractional anisotropy (FA)—a measure of the degree of water movement through myelinated axons—has also been shown to differ in people with ADHD, specifically being lower, indicating either less myelin or more axonal branches, in various neocortical regions (Ashtari, et al., 2005), especially in bilateral orbitofrontal regions (Konrad, et al., 2010), and the cerebellum (Castellanos, Giedd, Berquin, Walter, Sharp, & Tran, 2001). Different diagnostic tests for ADHD also correlate well with certain observed white matter abnormalities. Scores on the Conners' Inattentive Subscale (CAD), for example, show strong negative correlations with FA in the cerebellum (Ashtari, et al., 2005). Other research has found increased FA in other areas of the brain, namely in the right inferior parietal and occipitoparietal areas, and left inferior frontal and inferior temporal areas (Silk, Vance, Rinehart, Bradshaw, & Cunnington, 2009), suggesting either increased myelination or decreased axonal branching in the given tracts. It is important to note, however, that FA can also be affected by intra/extracellular volume changes or membrane permeability, so abnormalities observed in given tracts may not be due to problems with myelination. FA perfusion studies—indicating the mL of blood flow/gram of tissue/minute—have also found abnormalities. O'Gorman et al. (2008) found that perfusion in the left caudate nucleus and several frontal and parietal regions is higher in adults with ADHD, which is opposite to that found in children with ADHD, possibly indicating a long-term brain adaptation in the adults. The researchers were careful, however, to point out that such an increase in perfusion might have been due to chronic stimulant treatment, as the study's

participants were not drug naïve. Blood consumption increases have also been observed in the left inferior parietal/postcentral gyrus, an abnormality also seen in autism spectrum disorders (Brieber, et al., 2007).

The purpose of the current study was to analyze whether or not specific brain structure abnormalities have been consistently identified across a selection of ADHD imaging studies. To accomplish this, a meta-analysis was performed on several voxel-based morphometry (VBM) studies. VBM is a fairly new technique used to provide insight into both the structure and function of the brain. By taking several MRI “snap-shots” of a brain from many angles, voxels (i.e. volumetric pixels) of the images can be organized to provide a three-dimensional model of the brain of interest. This model can then be compared to control models to provide the precise Cartesian coordinates of abnormalities, such as tissue-volume or activation differences. The current study will focus on identifying differences in white matter and grey matter volumes in ADHD patients relative to healthy controls. As the frontal lobe, particularly the prefrontal cortex, is known to play roles in the mediation of attention and in decision-making, it is hypothesized that volume depletion will be identified in this area, especially in the white matter tracts which connect the prefrontal cortex to the basal ganglia. On account of its role in integrating stimuli with memory, it is also hypothesized that abnormalities will be found in the temporoparietal association cortices, specifically grey matter reduction. Finally, due both to its involvement with wide-spread brain activity and previous research (Castellanos, Giedd, Berquin, Walter, Sharp, & Tran, 2001), it is hypothesized that grey matter reductions will be observed in the cerebellum.

Materials and Methods

An extensive search for relevant ADHD articles was performed using the PubMed database. Search criteria were limited to primary analyses of brain structure and reviews of brain structure literature. The criteria for inclusion in the meta-analysis were that a study be written in English, that a study performed a whole-brain MRI analysis using a VBM approach and compared ADHD patients to controls, that a study reported p -values for VBM findings at a significance level of 0.05 or less, and that coordinates were given in either Talairach or Montréal Neurological Institute (MNI) space. Search terms used were ‘ADHD and grey matter’, ‘ADHD and white matter’, ‘ADHD and MRI’, ‘ADHD and imaging’, ‘ADHD and morphometry’, ‘ADHD and structural’, and ‘ADHD and voxel-based morphometry’. Out of 274 articles identified with these search terms, seven qualified for use in the meta-analysis and are summarized in Table 1. Three studies performed basic VBM analyses and were used to quantify grey matter, three studies applied a VBM approach to FA analyses and were used to quantify white matter, and one study performed VBM measurements that were usable in both the white matter and grey matter analyses. The final subject populations for the FA analysis were ADHD: $n = 84$ and control: $n = 76$, and for the grey matter analysis were ADHD: $n = 62$ and control: $n = 74$.

The data were processed using Signed Differential Mapping (SDM) software (<http://sdmproject.com/>), which differentially weighs various participant groups in order to calculate average values for statistically significant structural abnormalities found across multiple studies. Coordinates extracted from the studies were reported as significant at $p \leq 0.05$ and were in either Talairach space or MNI space, or had been converted by a paper’s authors from MNI space to Talairach space. No conversions were performed on the extracted

coordinates as SDM is programmed to perform the appropriate conversions and report findings in Talairach space. VBM coordinates were organized into a data table using Excel and global grey matter volumes were calculated to compare grey matter volumes. The data were then pre-processed, which generated SDM maps for each study and then randomized the coordinate locations multiple times in order to estimate the statistical threshold for chance. Pre-processing used 500 randomizations and was followed by mean analyses. Findings were considered significant at a threshold of $p \leq 0.05$. Findings were visualized with MRICron (<http://www.cabiatl.com/mricro/mricron/index.html>), and as MRICron templates are in MNI space, a Talairach underlay was used in order to produce accurate images. The same procedures were performed with FA coordinates.

Results

FA values were found to be lower in ADHD patients than in controls in the right anterior temporoparietal cortex, the left occipitoparietal cortex, the left dorsal parietal lobe, the right dorsal posterior frontal lobe, and both anterior medial temporal lobes (Figures 1 & 2). FA values were found to be higher in the right occipitoparietal cortex, the left anterior occipital lobe, the right medial prefrontal cortex, the prefrontal cortex, and the medial occipital lobe (Figures 3 & 4). Table 2 summarizes the FA analysis data. Coordinates given are the approximate center of identified abnormal areas (Radua & Mataix-Cols, 2009).

Grey-matter volume was found to be lower in the right inferior prefrontal cortex, the left anterior cerebellum, the posterior inferior temporal lobes, and the left sensorimotor cortex (Figures 5 & 6). Grey-matter volumes were found to be higher in the right medial posterior frontal lobe, the left lateral posterior frontal lobe, the left posterior parietal lobe, right anterior parietal lobe, the right posterior occipital lobe, and the left anterior temporal lobe (Figures 7 & 8). Table 3 summarizes the grey matter analysis data. As with the FA data, coordinates given are the approximate center of identified abnormal areas.

Discussion

I hypothesized that there would be white matter reduction in the prefrontal cortex, grey matter reduction in the temporoparietal association cortices, and grey matter reduction in the cerebellum. The meta-analysis confirmed at least one, and possibly two, of my hypotheses. Grey matter reduction was observed in the left anterior cerebellum, and the lower FA values observed in the prefrontal cortex correspond to tracts that connect the prefrontal cortex to the basal ganglia, suggesting a decrease in myelination of said tracts. Grey matter reduction was also observed in the prefrontal cortex. While my prediction of decreased temporoparietal grey matter was not confirmed, lowered FA values in the right temporoparietal cortex suggest white matter deficits in that area. These findings are consistent with brain areas previously theorized to participate in attention processes (Castellanos, Giedd, Berquin, Walter, Sharp, & Tran, 2001; Ashtari, et al., 2005; Konrad, et al., 2010). Other differences that were found but not predicted were lower FA values in the left occipitoparietal, dorsal parietal, and medial occipital cortices, and higher FA values in the right dorsal posterior frontal, right medial prefrontal, right occipitoparietal, and left anterior occipital cortices, as well as in the anterior medial temporal lobes. Grey matter volumes were also found to be lower in the anterior inferior temporal lobes, but were larger in the right medial posterior and left lateral posterior frontal lobes, the right anterior occipital lobe, the left anterior temporal lobe, and the posterior parietal lobes.

Many of the additional areas identified by this meta-analysis make sense conceptually as potential locations where abnormalities in structure or function might give rise to or exacerbate ADHD symptoms. The anterior and medial areas of the occipital lobes, for example, are part of the primary visual cortex (Brodmann, referenced in Gazzaniga, Ivry, & Mangun, 2009), and problems in these areas may make attending to visual stimuli more difficult as the stimuli would

not be processed properly in the first place. These areas also help guide visual attention, so deficits in these areas might also affect attention directly. Similarly, the occipitoparietal/parietal areas and the inferior temporal areas comprise, respectively, the “where” and “what” pathways for visual perception (Ungerleider & Mishkin, 1982), and problems in either or both of these pathways may produce deficits in visual perception of stimuli that can superficially resemble a lack of attention, or have secondary effects on attention. While these ideas are only speculative, they would make good hypotheses for future studies. For example, one could use functional MRI to investigate activation abnormalities in the “where” and “what” perceptual areas of the brain by comparing ADHD patients to controls while they locate items in space or identify briefly presented images.

It is important to note the ambiguity that is associated with the measures that were used in the meta-analysis studies. First, FA values are a measure of water movement through neuronal axons, and a low FA value can indicate either decreased myelination or increased axonal branching; conversely, high FA values can indicate either increased myelination or decreased axonal branching. This means that a given FA value, high or low, can potentially indicate an *improvement* in brain structure or function just as easily as a deficit. Combined with the fact that FA values can be affected by other factors such as membrane permeability, this reduces FA’s explanatory capacity and limits it to identifying potential avenues of inquiry that can be pursued with more decisive measuring procedures. It is important to keep in mind, however, that FA values do indicate some kind of white matter differences between ADHD patients and controls.

The observed grey matter differences also raise questions. While it is fairly straightforward to envision how decreases in grey matter may play a role in ADHD, it is not so clear how increases in grey matter might influence ADHD symptoms. One possibility is that

increases in some grey matter areas may have arisen as a result of long-term medication use (O'Gorman, et al., 2008). Conversely, over-development of or anatomical changes in some brain areas may be a form of natural compensation for under-development in others. Even though most of the ADHD patients in the studies analyzed were children and young adolescents (<16 years of age) and it is possible that insufficient time may have passed for such compensation to arise, brain development is extremely rapid in the first years of life and compensatory changes could have already taken place. I have conceived of two other possibilities, the first involving the neurons themselves. As surface area of an object increases linearly, its volume increases exponentially, which can cause transit problems if something needs to travel into or through said object. Overcoming this volume-to-surface area ratio problem is the reason eukaryotic cells, unlike bacteria and archaeia, use organelles and intracellular transport systems; with cells of such relatively large size, it is easier to maintain the necessary substrate concentrations if said concentrations and the processes associated with them are localized. Increases in grey matter concentration may be a result of neuronal somas getting too big, which could slow down substrate transport and subsequent metabolic processes, resulting in deficits. The second possibility involves glial cells, specifically astrocytes. One function that astrocytes perform is that of cleaning excess neurotransmitters out of synaptic clefts (Fields, 2009). Increased grey matter may actually indicate higher than normal numbers of astrocytes; with too many astrocytes in dopaminergic areas of the brain, for example, dopamine might end up being vacuumed out of the local synaptic clefts too quickly, giving rise to symptoms associated with a dopamine deficiency.

As of this writing, only one meta-analysis of the ADHD brain structure literature has been published. Valera, Stephen, Murray, and Seidman (2007) performed a meta-analysis on 21

MRI studies and identified significant ($p < 0.001$) volumetric reductions in the posterior cerebellum, the posterior corpus callosum, and the right caudate nucleus, as well as total volumetric reduction in the right cerebral hemisphere. They also identified some evidence of prefrontal and frontal volume reductions, though these were only found in two of the studies they analyzed. Additionally, they did not find significant volume differences in the left cerebral cortex, most prefrontal areas, or the anterior cerebellum. While there appear to be few overlaps between their meta-analysis and mine, it is important to note that their analysis did not include VBM studies, making cross-comparisons difficult. Valera et al.'s meta-analysis also aimed to identify volume differences at a p -value of 0.001, whereas I chose to use a more lenient p -value of 0.05. Valera et al. also point out that interpretations of their data must be made with caution, as the studies that they used often performed their measurements in different ways, making comparisons difficult and raising the possibility that some of their findings may not be accurate. VBM is a more standardized approach, and the differences in processing between studies are not as substantial as those in the Valera meta-analysis. Differences among participants, such as various comorbidities, may have also impacted on their results. While subject differences are problematic for all meta-analyses, the uniformity of the measures in the studies I used makes my approach an improvement over that of Valera et al.

Several factors should be noted as potential confounds in this meta-analysis. One is publication bias, which is a common risk when performing a meta-analysis. This can be mitigated somewhat in future studies by contacting individual researchers and requesting access to any unpublished data that they may possess. Lack of power is the second potential confound of note. VBM was developed fairly recently and is only now becoming a commonly used technique. This is likely to cause the overall number of subjects and number of studies in any

VBM meta-analysis to be moderate at best, which weakens subsequent statistical calculations. Many studies also limit their VBM measurements to specific regions of interest (ROIs) that have been previously shown to correlate with whatever the given study is researching. Since the current meta-analysis only included studies that performed whole-brain VBM analyses, the number of applicable studies was diminished even further, providing a relatively modest sample of participants and controls (FA analysis: ADHD: $n = 84$, control: $n = 76$; grey matter analysis: ADHD: $n = 62$, control: $n = 74$) and lowering the overall power of the meta-analysis. The diminished power of the meta-analysis is made apparent when the threshold is changed from $p = 0.05$ to the more conservative $p = 0.001$. At a $p = 0.001$, only negative values are identified, and in only three small areas: grey matter decrease in the right caudate and the left anterior occipital lobe, and a stretch of white matter in the right temporoparietal lobe. Each of these areas were subsumed into larger clusters at a p -value of 0.05. Only an increase in the number of studies that use a VBM approach can ease this problem of diminished power.

Comorbidities among the ADHD populations present in the meta-analysis studies present another problem. While some studies, such as that by van 't Ent et al. (2008), made an effort to minimize the presence of secondary neurological or psychiatric conditions in the ADHD population, others did not, nor were comorbid conditions balanced across control groups. The existence of additional pathologies makes interpretation of the structural findings difficult, especially as ADHD is often accompanied by one or more of a regular group of problems, such as Tourette's syndrome or depression (Purper-Ouakil, Ramoz, Lepagnol-Bestel, Gorwood, & Simonneau, 2011). This in turn raises the question of whether a given structural finding is due to ADHD rather than a common comorbid disorder (Yang, Wang, Chuang, Jong, Chao, & Wu, 2008), though one of the strengths of a meta-analysis over a study with a small number of

subjects is its stronger resistance to variance on account of subject differences. The problem of comorbidity can be particularly challenging, as controlling for given comorbidities can decrease the number of ADHD patients that can be included in a study, which then raises the previously discussed issue of diminished power.

Participant age is another shortcoming of this meta-analysis. With the exception of Konrad et al. (2010), all of the studies included in the meta-analysis involved participants 18 years of age or younger. As noted in Valera et al. (2005), having such a small adult population makes it all but impossible to gain insight into the developmental trajectory of ADHD. As ADHD symptoms are known to change over time, in both intensity and nature (Konrad, et al., 2010; Biederman, 2005), it is reasonable to hypothesize brain structure differences between young ADHD patients and older ADHD patients. Unfortunately, the relative dearth of adult brain structure data in the ADHD literature makes such differences difficult to identify. Sex provides a similar difficulty, as males and females with identical ADHD symptoms have been shown to possess different structural and functional brain deficits (Yang, Wang, Chuang, Jong, Chao, & Wu, 2008; Castellanos, Giedd, Berquin, Walter, Sharp, & Tran, 2001). As such, combining males and females into the same patient group, which all of the studies in the meta-analysis that contained females did, makes subsequent interpretation of any findings problematic. Future studies should make an effort to group males and females separately, in order to provide clearer insight into the sexually dimorphic characteristics of ADHD.

In conclusion, the current meta-analysis identified widespread grey matter and white matter abnormalities in ADHD patients. Many of the brain areas where abnormalities were identified, such as the pre-frontal cortex, are consistent with previous findings, though a few, such as areas of the anterior cerebellum, contradict the current literature. From a functional

standpoint, several of the regions identified are known to be involved in attentional processes. Additional areas, however, such as those of the occipital lobes, are not normally implicated in the ADHD literature, and their presence among the results may be due to idiosyncracies in the current data set, such as the previously discussed comorbidities. It should also be noted that none of these unexpected regions are significant at a $p = 0.001$.

The most important goal of future brain imaging research needs to be a greater focus on indentifying the catagorical details of ADHD. Identifying structural and functional differences between age groups and the sexes will provide valuable insight into how various brain abnormalities mediate ADHD symptomatology in different groups. Controlling for comorbidities should also be a concern for future research. While eliminating all ADHD patients with any comorbid disorders from a given study will likely render the subject group so small as to provide inconclusive results, efforts should be made to group ADHD patients with their comorbidities in mind; placing ADHD patients with mood disorders in one group and ADHD patients with Tourette's syndrom in another, for example. Similarly, medication history should be taken into account when grouping participants for inclusion in future studies, as it is possible that medication can have long-term effects on the brain (O'Gorman, et al., 2008). Patients should also be grouped by ADHD subtype; whether or not the inattentive subtype truly is a separate condition (Carmona, et al., 2005), the simple presence of symptoms distinct enough to call for separate catagories suggests the possibility that brain abnormalities might differ between subtypes. For example, inattentive ADHD might correlate with abnormalities in the the primary visual cortex, while hyperactive ADHD might correlate with structural or functional abnormalities in the motor cortex, to name just two areas that were identified in the current meta-analysis. Making greater use of a whole-brain VBM approach to brain imaging would also be

helpful for future research, as it will add studies to the imaging literature that can be more easily compared to each other. It is important to not only be as detailed as possible in our scrutiny of different ADHD populations for group differences, but to also use every tool and technique at our disposal as we do so. By approaching ADHD in this detailed and discriminating manner, we improve our chances of not only learning about ADHD pathology in general, but we also improve our view of ADHD as it is experienced by different people, and it is this view that will best inform our decisions regarding individual diagnoses and treatments.

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