META-ANALYSIS: MRI VOLUMETRIC DATA OF CHILDREN
WITH ADHD SUBTYPES

by

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ABSTRACT

Attention-deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder consisting of inattentive and/or hyperactive behaviors that is typically prevalent in childhood. There are three recognized subtypes of this disorder—hyperactive, inattentive, and combined. The current study’s purpose is to examine how the subtypes differentiate based on brain structure volume size. There have been studies on ADHD subtypes and brain structure volumes in children, but there are a number of limitations in available research that make it difficult to generalize findings. A meta-analysis was done using 8 studies that included volumetric data of ADHD subtypes (inattentive and combined) in children that was acquired through magnetic resonance imaging (MRI) techniques. Analyses were done looking at combined and inattentive type in comparison to controls and between the two groups. Further subgroup analyses were done on gender and brain regions in the two subtypes. Results show that there is a significant brain volume reduction in combined type in comparison to controls and inattentive type. There is also a significant volume reduction observed in males. The other analyses done yielded insignificant findings, although the volume reduction in inattentive type was only slightly above the cutoff of alpha (0.05). These findings help in better understanding the relations between brain volume and ADHD subtypes, but further research is still needed in this area.

Keywords: ADHD, combined, inattentive, MRI, brain volume

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Meta-Analysis: MRI Volumetric Data of Children with ADHD Subtypes

Attention-deficit hyperactivity disorder (ADHD) is neurodevelopmental disorder with a typical onset in childhood or early adolescence. The disorder consists of patterns of inattentiveness and/or hyperactivity. With three categorical subtypes (inattentive, hyperactive, and combined), there are a number of ways this disorder can manifest in an individual (American Psychological Association [APA], 2013). Although the exact prevalence is unknown at this time, it is estimated that 8.4% of children in the United States have a current diagnosis of ADHD (Children and Adults with Attention-Deficit/Hyperactivity Disorder [CHADD]; n.d.). There are not accurate estimates available for the prevalence of the individual subtypes.

Children with ADHD experience a number of deficits and impairments in cognitive, behavioral, and emotional functioning (Brown, 2002; Kaiser et al., 2015). Some of these core deficits are also apparent across the subtypes (Mayes et al., 2009; Kaiser et al., 2015). Although there is extensive research available on ADHD, there is still a lot that is unknown. Research has unveiled that ADHD has neuroanatomical underpinnings. This is validated by studies examining brain regions in relation to ADHD. Research has provided evidence that there are structural brain differences in individuals with ADHD, typically in the form of decrease in structural volume sizes (Vilgis et al., 2015; Carrey et al., 2012). Less is known about structural differences in the subtypes in children since this area is less

frequently examined in its entirety. Current research on the subtypes has found mixed results, with some reporting volume decrease, some reporting volume increase, while others report no differences in volume size at all (Vilgis et al., 2015; Al-Amin et al., 2017; Bledsoe et al., 2009; Pineda et al., 2002).

It is important to further understand the areas that are affected in relation to the subtypes and the clinical implications this could have. The disorder has a high prevalence and the use of the subtype classification is the current diagnostic practice. Structural data could expand on the understanding of ADHD subtypes, confirm the current classification system, act as a diagnostic tool, and aid in treatment planning.

Literature Review

Attention-Deficit Hyperactivity Disorder (ADHD)

ADHD is a neurodevelopmental disorder recognized by the Diagnostic and Statistical Manual-5 (DSM-5). The DSM-5 classifies ADHD as a persistent pattern of inattention and/or hyperactivity that interferes with functioning or development. The DSM-5 has defined inattention as having such traits as not giving close attention to details, difficulty sustaining attention to tasks, and not listening when spoken to. Hyperactivity and impulsivity have been defined as, but not limited to, exhibiting frequent fidgeting, inability to remain seated, and running and climbing when inappropriate (APA, 2013).

In order to meet diagnostic criteria, six or more symptoms of inattention and/or hyperactivity and impulsivity need to be present for at least 6 months to a degree that is not appropriate for the developmental level the individual is at. The symptoms must impact functioning in at least two settings and be present to a large degree prior to age of 12 years (APA, 2013). Starting with the DSM-IV, ADHD was broken down into subtypes. Following this system, the DSM-5 offers three specifications under the ADHD diagnosis – combined presentation (C), predominantly inattentive presentation (I), and predominantly hyperactive/impulsive presentation (H; APA, 2013). ADHD-I diagnosis requires that the majority of symptomology falls under inattentiveness, whereas ADHD-H is predominantly hyperactive and impulsive behaviors. ADHD-C is a fair distribution

of impairments in attention and hyperactivity and is thought to be the most common subtype of the three (APA, 2013).

Since there are several variations in how this disorder can be classified, there are a number of developmental, emotional, and cognitive domains that are at risk for being impaired in children with ADHD. Executive functioning is one of the more frequent deficits observed in this disorder. Impairments of executive functioning can be broken down into 6 clusters (Brown, 2002). The clusters include activation, focus, effort, emotion, memory, and action. Activation is the difficulty in planning tasks, estimating time, and prioritizing. Focus entails difficulty in focusing, sustaining focus, or shifting focus from one task to another. Effort is the difficulty in alertness, effort, and processing speed. Emotion is the difficulty in managing frustration and regulating emotions. Memory is the difficulty using working memory and recalling information. Action is the challenge in monitoring and regulating one's actions (Brown, 2002).

ADHD has a major impact on the performance in school settings. Children with this disorder have been found to have slightly lower intelligent quotients (IQ) than comparison groups (Biederman et al., 2012). ADHD affects academic achievement over the course of development, with untreated groups performing at lower standards than those receiving treatment and typically developing children (Arnold et al., 2015).

Across all settings, a large proportion of Children with ADHD have deficits in fine and gross motor skills (Kaiser et al., 2015). They also display slower speeds in motor activation (Borger & Meere, 2000). Children with ADHD are also more likely to experience sleep disturbances, such as problems falling and remaining asleep (Stein, 1999).

There are differences in how ADHD symptomology manifests dependent on gender. School-aged children with ADHD differ in classroom behaviors based on gender. Girls are more likely to be verbally aggressive, whereas boys demonstrate higher rates of rule-breaking and externalizing behavior (Abikoff et al., 2002). Physical aggression is higher in boys with ADHD than girls (Carlson et al., 1997). Boys with higher rates of combined and hyperactive-impulsive subtypes have a higher degree of impairment in social functioning, academic performance, and self-esteem (Graetz et al., 2005).

Research has found a number of disparities in ADHD dependent on race and ethnicity. Minority children have been found to be less likely to be diagnosed with ADHD, with Black children being 70% less likely than White children to receive this diagnosis (Morgan et al., 2013; Morgan et al., 2014). Being raised in an English-speaking household has been found to be a risk factor that increases the chances of receiving an ADHD diagnosis, which is supported by the findings that Latinx/Hispanic children are less likely than White children to receive this diagnosis if they come from a non-English speaking household (Morgan et al.,

2013; Morgan et al., 2014). A factor found to decrease the chances of receiving an ADHD diagnosis is not having health insurance (Morgan et al., 2013). Racial and ethnic minority groups are less likely than Whites to be uninsured, and although this gap has drastically closed since the introduction of the Affordable Care Act, these differences are still present (Chaudry et al., 2019). Due to this, it is unclear if the data on the diagnosis of ADHD in racial and ethnic minority groups is an accurate reflection of the prevalence of this disorder or the result of inaccessibility. There has also been an observed difference in racial and ethnic minorities and the treatment they receive, with minority groups being less likely than Whites to take prescription medication for the disorder (Morgan et al., 2013).

There are observed differences in behavior when looking at the individual subtypes. Children with ADHD-I are less likely to experience sleep disturbances than those with ADHD-C (Mayes et al., 2009). Children with ADHD-I are more likely to demonstrate impairments in fine motor abilities, slower reaction times, and motor control in comparison to those with ADHD-C (Kaiser et al., 2015). Children with ADHD-C have higher rates of impairment in social functioning and pro-social behavior, and the tendency to be disliked by peers (Willcutt et al., 2012). Children and adolescence with ADHD-C are also more likely to be sustain injuries that require medical attention (1998, as cited in Willcutt et al., 2012).

ADHD is frequently diagnosed in combination with other developmental disorders at an estimated rate of 67% (Elia et al., 2008). Internalizing and

externalizing disorders are commonly observed with this disorder. Oppositional defiant disorder, mood disorders, and anxiety disorders are some of the more frequent disorders that co-occur with ADHD (August et al., 1996). Anxiety disorders are equally diagnosed with ADHD-C and ADHD-I (Elia et al., 2008). Oppositional defiant disorder, conduct disorder, and bipolar disorder are more frequently diagnosed with ADHD-C (Willcutt et al., 2012). Depressive disorder and learning disabilities are more commonly diagnosed with ADHD-I (Willcutt et al., 2012).

The behavioral patterns typically observed in ADHD have been shown to change dependent on the comorbid disorder. Children with ADHD in combination with oppositional defiant disorder or conduct disorder have higher rates of impulsivity, while children with ADHD and anxiety disorders demonstrate an increase in inattentiveness (Newcorn et al., 2001).

There are several pharmaceutical and behavioral treatments available for ADHD. Although there are several options available, stimulant medication is the most common method to treat this disorder in children (Bussing & Gary, 2009). Methylphenidate is one of the more commonly prescribed medications for treating ADHD. While it has been found to help reduce the undesirable behaviors commonly seen in this disorder, it poses a risk of having adverse side effects (Wilens et al., 2005). The side effects can include emotional outburst, difficulty falling asleep, decrease in appetite, and irritability (Wigal et al., 2006). There is

also a higher prevalence of severe sleep problems in children with ADHD who are taking stimulant medication (Stein, 1999).

There are a wide range of behavioral treatments available for ADHD. Treatments might focus on child training, parent training, classroom management, or peer interventions. The goal of such treatments is to modify behavior in home, classroom, or other settings, as well as in peer interactions (Subcommittee on Attention-Deficit/Hyperactivity, 2011). The different models have been found to effectively treat behavioral impairments, such as externalizing, hyperactivity, inattentiveness, opposition, emotional regulation, and social functioning (Subcommittee on Attention-Deficit/Hyperactivity, 2011; Webster-Stratton, 2011).

Research has demonstrated that there are a number of core deficits in ADHD. These impairments, although disproportionate from one another, still exist at the subtype level. ADHD symptomology has also been shown to be sensitive to gender, comorbidity, and treatment. Based upon the commonality in behavioral deficits observed in ADHD, it strongly suggests there are neuroanatomical underpinnings in this disorder.

There are several ways to assess ADHD in the pediatric population. Since ADHD impacts functioning in multiple settings, it is common to perform assessments in home and school settings in order to get an accurate picture of how the disorder manifests in each individual. Developers have created valid and reliable measures to assess ADHD across the developmental lifespan. The Behavior

Rating Inventory of Executive Function (BRIEF) and Behavior Assessment System for Children (BASC) are two of many accepted measures used to assess ADHD in children (Jarratt et al., 2005). Assessments can be done through such methods as clinician interviewing, parent reports, self-reports, and teacher reports. Although these measures tell us what is happening on a behavioral level, they give little to no information on what is occurring on a neuroanatomical level. Since ADHD is a neurodevelopmental disorder, it is important to take into consideration what has been impacted in brain regions to give us the behavioral impairments that are observed in this population.

Magnetic Resonance Imaging (MRI)

An MRI is a medical imaging technique. It uses a magnetic field and computer-generated radio waves to create images of the body. Most machines are large, tube-shaped magnets that a person lies inside of. The magnetic field temporarily realigns water molecules in the body. Radio waves cause these aligned atoms to produce faint signals that are used to create cross-sectional images. The result is a set of high-resolution images of targeted areas of the body. The images are used to help diagnose a number of problems (Mayo Clinic, n.d.). Figure 1 shows the type of images that are produced using MRI machinery.

Figure 1

MRI Scan of Healthy Child

Note. This image was taken from kidshealth.org. It is an image of a MRI scan done on a child and shows the images produced from MRI devices.

Volumetric Findings

MRI scans have made it possible to understand what is occurring in ADHD on a neuroanatomical level. ADHD has been associated with low global and white grey matter in the frontal, right parietal, and right temporal regions (Vilgis et al., 2015). Researchers have been able to discriminate between ADHD and control

subjects 73.7% of the time while looking at MRI scans. This accuracy was due to differences in the cortical shape in the left temporal lobe, bilateral cuneus, and regions around the left central sulcus (Sun et al., 2018). ADHD has also been associated with reductions in the caudate, globus pallidus, and thalamus (Rosch et al., 2018). Although there is extensive data supporting brain structure abnormalities in ADHD, it is important to analyze if these differences still exist when looking specifically at the ADHD subtypes.

Although there are 3 ADHD subtypes, prior studies have chosen to exclude ADHD-H from their sample due to low prevalence (Huang et al., 2017). This decision is supported by research that has found that there is little evidence of validity of ADHD-H after the first grade (Willcut et al., 2012). Although the hyperactive-type is not supported, neuropsychological testing supports the discrimination between ADHD-C and ADHD-I (Lockwood et al., 2001).

Prior research has used MRI scans to gather volumetric data on brain structures of individuals with ADHD subtypes (Farmer, 2002; Bledsoe et al., 2009; Sun et al., 2018). There are various methods to collect volumetric data using MRI scans. Figure 2 is a demonstration on how authors in one study calculated this information (Al-Amin et al., 2018). Some studies have found that children with ADHD-C have smaller volumes of the caudate nucleus and anterior cingulate cortex (ACC) compared to ADHD-I (Semrud-Clikeman et al., 2017; Carrey et al., 2012). Contrary to these findings, another study reported that the left caudate

nucleus head volume was significantly larger in the left side in both ADHD-C and ADHD-I in comparison to controls, but this relation was not found between the two ADHD groups (Pineda et al., 2002). Age has been found to be a predictor of volume size in the right caudate nucleus, with younger age being associated with smaller volume sizes in this structure (Vilgis et al., 2016). The caudate nucleus has been linked to areas of learning, such as storing and processing of memories, and the anterior cingulate cortex is associated with complex cognitive functions, such as empathy, impulse control, emotion, and decision-making (Heathline, 2015; Neuroscientifically Challenged, n.d.).

Figure 2

Example of How Volumetric Data is Collected Using MRI Scans

Note. This image was taken from Al-Almin et al. (2018). It demonstrates how the volume of hippocampal regions were calculated using MRI scans in children with ADHD. CA= cornu ammonis; GC-DG= granule cell layers of the dentate gyrus; HATA= hippocampus-amygdala-transition-area.

It has also been found that individuals with ADHD-C are more likely to have reductions in hippocampal volumes and a smaller posterior inferior vermis (Al-Amin et al., 2017; Bledsoe et al., 2009). The hippocampus is associated with learning and memory, while the posterior inferior vermis is linked to coordination and movement (Cherry, 2019).

It was found that in both combined and inattentive type, there were significantly lower global and local gray matter volumes in frontal, right parietal, and right temporal regions in comparison to typically developing children, but not between the two subtypes (Vilgis et al., 2016). Farmer (2001) found that children with combined type had smaller volumes in the right prefrontal dorsolateral and left parietal regions in comparison to controls, whereas inattentive type experienced decreases in the right parietal and bilateral prefrontal dorsolateral regions. The areas found to be impacted in both studies have been linked to a number of behaviors and cognitions, many of which have been associated with ADHD. Gray matter in the brain has been associated with sensory control and muscle activation (The Human Memory, 2019a). The frontal lobe has been linked to such tasks as spatial orientation, emotional expression, problem solving, judgment, impulse control, and interpreting feedback from the environment (Centre for Neuro Skills, n.d.). The parietal lobe plays an important role in spatial relations and interpreting pain and touch (The Human Memory, 2019b). The temporal lobe has been associated with such things as listening, processing sensory information, and

emotional control (The Human Memory, 2019c). While a number of studies reported significant findings in differences in brain volumes, one study found no difference in the volume sizes of the brains of children with ADHD subtypes (Sun et al., 2018).

Researchers have been able to discriminate between ADHD-I and ADHD-C 80.1% while looking at MRI scans due to alterations in the default mode network and insular cortex (Sun et al., 2018). The default mode network is an interconnected group of brain structures and the insular cortex has been associated with linking sensory experience and emotional valence, motor control, self-awareness, and social functioning (Neuroscientifically Challenged, 2015; Gogolla, 2017). Additional research has sought to use classification software to identify ADHD-C and ADHD-I. When doing so, they found differences in the surface area of the frontal lobe and the cortical thickness, volume, and average surface area of the entire cortex (Qureshi et al., 2016).

There have been differences found in the brain volumes of children with ADHD dependent on gender. Boys with ADHD-C experience a decrease in the volume of the ACC in comparison to typically developing boys, whereas girls with ADHD-C experience an increase in the volume of the ACC in comparison to typically developing girls (Villemonteix et al., 2015). Boys with ADHD have also been shown to have smaller accumbens, amygdala, and hippocampus volumes

compared to typically developing boys, but these relations were not found in girls (Wang et al., 2018).

Comorbidity has been shown to have an impact on the brain volume abnormalities seen in ADHD. Children with ADHD-C and ADHD comorbid with conduct-disorder have similar brain volume abnormalities (Bussing et al., 2009). Both groups experience smaller volumes in the left and total posterior superior and inferior lobes of the vermis in comparison to healthy controls; however, there is not a significant difference in volume when comparing the two groups to one another (Bussing et al., 2009).

Taking a further look into comorbidity, one study examined the interaction between ADHD and bipolar disorder (Biederman et al., 2008). A sole diagnosis of bipolar disorder was linked to smaller orbital prefrontal cortex and larger right thalamus. These findings were still present in subjects with ADHD plus bipolar disorder. A sole diagnosis of ADHD was associated with a decrease in grey matter, frontal lobe and prefrontal cortex volumes, and the right ACC. This was also observed in the comorbid group. These findings show that the volumetric abnormalities specific to the individual disorders continue to persist in cases of comorbidity (Biederman et al., 2008). This suggests that if volumetric data is collected, this consideration should be kept in mind due to the potential effects it can have on the findings.

Treatment has been found to impact brain volume in children with ADHD. When looking at children who had taken stimulant medication in relation to those that did not, both groups experienced a decrease in the volume of the caudate when compared to healthy controls. However, the right ACC was significantly smaller in treatment-naïve groups in comparison to those that received treatment (Semrud-Clikeman et al., 2006). Children with ADHD who were never medicated are more likely to have smaller cerebral, cerebellar, and white matter volumes compared to medicated children and controls (Castellanos et al., 2002). Since treatment in the form of medication has been shown to impact the volume size in the brains of children with ADHD, this is also important to take into consideration when collecting data of this nature.

Although there is available research on the ADHD subtypes and volume of brain regions, the studies are scarce, some of the studies used smaller samples, and different regions of the brain were analyzed. Some studies only include volume data, but offer no analysis, while others report results where other measuring techniques were layered with MRI scans. There have also been inconsistencies in the findings, with some studies reporting that they found no differences in the brains of children with ADHD-C and ADHD-I (Vilgis et al., 2015). Due to these reasons, available findings would benefit from a meta-analysis. Conducting this type of analysis would help determine the strength of prior findings and make the findings more generalizable.

Meta-Analysis

A meta-analysis is the statistical analysis of a collection of results from individual studies with similar hypotheses for the purpose of combining the findings (Glass, 1976). In research, it is common for multiple studies with the same or similar hypotheses to be released because researchers are unaware of what others are doing, researchers are skeptical about prior findings, or researchers wish to strengthen previous findings (Cooper et al., 2009). The purpose of a meta-analysis is to establish generalizations of prior findings or the lack thereof (Cooper et al., 2009). In order to do a meta-analysis, effect sizes need to be collected.

An effect size refers to the size of a relationship between two variables (Cooper et al., 2009). It is to be used to quantify the relationship between two variables (Cooper et al., 2009). When determining an effect size index, effect sizes from different studies should be comparable, substantively interpretable, computable from information likely to be reported in published reports, and good technical properties (Cooper et al., 2009). Once the effect sizes are computable, a fixed or random effects model should be employed. For the purpose of this study, a random effects model is more appropriate.

A random effects model is used for combining effect sizes under which observed effect sizes may differ from each other because of both sampling error and true variability in population parameters. This model provides predictions of what the results might have been of a meta-analysis if the studies were done with

other participants, and also if the treatment, setting, or outcome measures were changed (Cooper et al., 2009).

An important consideration to take into account in a meta-analysis is that there might be variability across studies based on the characteristics included. Variability across the studies is called heterogeneity. If heterogeneity is found to be significant, a moderator analysis should be done to account for variability in the findings (Cooper et al., 2009).

A moderator analysis examines the impact that moderator variables have on the observed effect sizes. Moderators are defined as variables that could be contributing to the effect sizes. In order to do this, models are estimated for the variables of interest and compared to one another (Cooper et al., 2009).

One major issue in working with research and doing a meta-analysis is a phenomenon called publication bias. A publication bias is the likelihood that a study with statistically significant results is more likely to be published than a study with non-statistically significant results. Studies with statistically significant results are more frequently cited and likely to be published in well-known journals. Publication biases could potentially compromise the validity of a meta-analysis. Due to this, research syntheses that fail to include unpublished studies may exaggerate the magnitude of a relationship (Cooper et al., 2009).

Current Study

Since there is limited data available that examines volumetric data gathered from MRI scans in relation to ADHD subtypes in children, this study aims to do a systematic review of prior research. For the purpose of this study, ADHD-H will be excluded from further analysis since there is limited to no data provided for this classification and research does not support it. The current study will include the data of research done on samples that include at least some children. All participants in the studies included need to have a current diagnosis of ADHD with a subtype specified according to DSM-5 standards, or whichever edition was relevant at time of data collection. This study will only look at samples who are not receiving treatment or taking medication due to the effects this could have on the volumetric data. In addition to this, the current study will only examine a sole diagnosis of ADHD with no comorbidity to ensure findings are not impacted by another disorder.

The field of psychological assessment, treatment, and research will greatly benefit from this analysis. The current study will help determine the strength of prior findings and make them generalizable. The findings will also help determine if the current DSM-5 criteria is a strong diagnostic tool. In addition to this, a better understanding of areas of the brain affected by ADHD could help aid in the development of a more personalized treatment plan. Knowing more about the developmental trajectory of the disorder will aid in the response efforts. In order to

a detailed account of this information, a closer analysis will be done looking at the differences between the subtypes and data of specified brain regions.

Based on the data and findings of prior research on ADHD subtypes and brain structure volumes in children, the following hypotheses have been set for the current study:

Hypothesis 1: Children with ADHD-C will experience a
decrease in brain volume size

Hypothesis 2: Children with ADHD-I will experience a
decrease in brain volume size

Hypothesis 3: Males will have a smaller brain volume size compared to
females

Hypothesis 4: There will be a difference in the volumes of the left and right
hemispheres of the brain in children with the ADHD
subtypes

Hypothesis 5: The caudate nucleus will be smaller in children with ADHD

Method

Search Strategies

In order to find studies with the same research question, searches were done on multiple medical and psychological databases (PsycINFO, ScienceDirect, SAGE Premier, Google Scholar, and PubMed). There was not a search criterion for date due to scarcity in this particular area of research. The final set of studies that were included ranged from 2002-2018. Since the DSM-IV-TR was the introduction of the ADHD subtypes, 1997 is the earliest a study would have been published. The search terms included: *MRI, magnetic resonance imaging, brain volumes, attention-deficit hyperactive disorder or ADHD, subtypes, ADHD-inattentive or ADHD-I, ADHD-combined or ADHD-C, and children.*

Eligibility Criteria

For inclusion in this study, the following criteria needed to be met: (1) The individual had to be diagnosed with ADHD, (2) have ADHD-I or ADHD-C as a specifier, (3) the study must include at least some children below age 18, (4) they currently are receiving no treatment, (5) the study was done between 1997 and 2019, and (6) there cannot be a comorbid disorder. For the purpose of this study, a comorbid disorder is defined as having one or more additional diagnoses beyond that of ADHD. Studies were excluded if they did not meet this inclusion criteria. The following were criteria for exclusion: (1) the study did not look at children, (2)

did not specify subtype, (3) was not published in English, and (4) individuals in the sample were in partial remission as defined by the DSM-5 specifier.

Data Abstracting and Coding

There was a total of 39 articles reviewed at the start of this study. Upon abstract review, 16 were excluded due to insufficient information relevant to this analysis. After full-text review, 8 studies were excluded. 7 were then excluded due to insufficient statistical information. After review, 8 studies were included in the final analysis that met all inclusion and exclusion criteria. The PRISMA in Figure 3 shows the process of selecting articles to include in this study.

Figure 3

Studies for Meta-Analysis (PRISMA) Chart of Literature Search for ADHD Subtypes and Volumetric Data of MRI Scans of the Brain

Software Analysis

The current study uses R software for all analyses done. R software has packages embedded in the program, each used to run a variety of statistical analyses on data. Although this study utilizes a number of packages, the main ones used are ‘metafor’ and ‘robumeta’. ‘Metafor’ was used since it was designed to determine effect sizes of random-effect meta-analysis models and allow for moderators to be considered in the analysis (Viechtbauer, 2010). ‘Robumeta’ was used since it can consider dependency amongst multiple effect sizes in a meta-regression model (Fisher & Tipton, 2015).

Statistical Analysis

This study is a quantitative meta-analysis since there is prior research on this topic that would greatly benefit from a systematic review. From the studies included in this analysis, the reported effect sizes were documented. Effect sizes were then converted to the same unit of measurement. While converting, a standardized index, effect sizes and standard error were calculated. The studies included in this analysis drastically vary in sample size. Effect sizes were computed to Hedge’s g since it accounts for difference between groups. This is similar to Cohen’s d ; however, Hedge’s g works better with smaller samples sizes (Hedges, 1981). The results were held to the following standards: small effect size= 0.2, medium effect size= 0.5, large effect size= 0.8.

Heterogeneity is the variability amongst the studies. To determine heterogeneity in this study, total variance and sampling error needed to be calculated. Q -statistic is total variance and df is sampling error. If Q is found to be much larger than df , we can assume heterogeneity. The test statistic used for this analysis is a chi-square. P -value is set at alpha level (0.05) for significance. If the p -value is found to be significant, we can conclude studies have systematic variability.

To determine the effects of variables, a moderator analysis will be employed for this analysis. There are a number of moderators considered for this study: (1) ADHD subtype, (2) gender (male or female), and (3) brain region. ADHD subtype was coded by ADHD-C and ADHD-I. Gender was coded according to percent of males in each study. This was done since there were far more males included in the studies. Brain regions were more complicated to categorize. The studies included all reported different regions of the brain, with minimal overlap. Grouping for further analysis of the brain regions was determined if the study reported the region as left or right, or the region appeared in three or more studies. Based on this consideration, analyses were done on left and right sides of the brain, and on left and right sides of the caudate nucleus. The relations of volume size within each subtype was looked at, then a comparison was done between ADHD-I and ADHD-C.

Results

Random Effects Model

For the final analysis, there were 8 studies and 95 effect sizes included. All effect sizes can be found in Figure 4 and detailed information about the studies are provided at Appendix A. In order to get the pooled effect size, a robust variance estimation (RVE) was done considering dependency amongst multiple effect sizes (Cooper et al., 2009). Results from this analysis can be found in Table 1. The pooled effect size was -0.163 with a non-significant p -value of 0.056. The p -value is only slightly over significance. Even though we found slightly insignificant research of effect sizes due to the small sample size, we assume there is some variability across the studies therefore a heterogeneity test and moderator analysis were conducted.

When testing for heterogeneity using a univariate random-effects model, the total variability is 66.31%. The Q -statistic for this analysis was found to be 239.271, df of 94, and a significant p -value of less than 0.001 indicating that there is heterogeneity across effect sizes. Based on the results, to explain the systematic variability, moderator analyses were conducted.

Table 1*Result of Pooled Effect Size with Robust Variance of Estimation*

	Effect Size	Standard error	<i>p</i> -value	<i>Q</i> -statistic
RVE	-0.163	0.070	0.056	239.271 ($p < .001$)

Forest Plot of Effect Sizes Included in Study

Moderator Analysis

A moderator analysis was done for the categorical variable of ADHD subtype. There were 52 effect sizes from 8 studies for combined type and 43 effect sizes from 6 studies for inattentive type. The pooled effect size for combined type was -0.256 with a significant p -value of less than 0.001. This supports hypothesis 1 in predicting children with ADHD-C would experience a brain volume reduction. The pooled effect size for inattentive type was -0.0579 with a nonsignificant p -value of 0.062. This does not support hypothesis 2 since a brain volume reduction in ADHD-I was not found. The Q -between test for subtype was 35.043. The p -value for Q -between was calculated comparing the two groups using a chi-square test, resulting in a significant value of less than 0.001 (see Table 2). This indicates that the two groups have statistically different pooled effect sizes.

Table 2

Results from Moderator Analysis with Type of ADHD (ADHD-I vs. ADHD-C)

	Effect Size	Standard error	p -value	Q -Between
ADHD Combined	-0.256	0.055	< 0.001	
ADHD Inattentive	-0.058	0.031	0.062	
ADHD-I vs. ADHD-C			< 0.001	35.043

A moderator analysis was done for percent of males included in the studies. The mean of proportion of males was found to be 0.795 (79.5%). The mean of males was centered for further analysis. This data was represented by an RVE meta-regression model treating centered gender as a moderator. The intercept for volume was 0.148 with a significant p -value of 0.022. This is the pooled effect size when the analysis has a mean level of proportion of males (79.5%). The coefficient for gender was -1.105 with a significant p -value of 0.024. These findings are in support of hypothesis 3 and indicate that there is a significant decrease in volume size in males. The results of the moderator analysis with gender can be found in Table 3.

Table 3

Results from Moderator Analysis for Gender

	Coefficient	Error	p -value
Intercept	-0.148	0.047	0.022
Gender (% of Male)	-1.105	0.240	0.024

Subgroup Analyses

Additional subgroup analyses were done on this dataset in order to determine if relations existed amongst variables included in each domain. There

was a large variation in brain regions reported in the studies included; therefore, it was difficult to break this information down to conduct a simple analysis. In order to use brain regions in an analysis, they were coded and grouped together in any combination that would make sense. Based on this, regions were coded by being specified by left or right hemisphere. They were also coded for left or right caudate nucleus since this was the most frequently reported structure, and prior research has reported findings in this region in relation to ADHD subtypes. An analysis was done for the brain regions looking at differences in each individual subtype, then by looking at the differences between the two subtypes.

When looking at the relations between the subtypes and the volumes of regions specified as being in the right or left hemisphere of the brain, hypothesis 4 was not supported since there were no significant findings (see Table 4). There were 11 effect sizes included for ADHD-C in the right and left hemispheres. ADHD-C in the right hemisphere had an effect size of -0.308 and a p -value of 0.089. ADHD-C in the left hemisphere had an effect size of -0.180 and p -value of 0.112. There were 9 effect sizes included for ADHD-I in the right and left hemispheres. ADHD-I in the right hemisphere had an effect size of -0.122 and p -value of 0.264. ADHD-I in the left hemisphere had an effect size of -0.166 and p -value of 0.104.

A further analysis comparing the groups yielded similar results, with no significant findings. When comparing ADHD-C in the right and left hemispheres,

the Q -Between was 0.041 with a p -value of 0.840. This indicates that there is not a significant difference between the two ADHD-C groups. The Q -Between for ADHD-I in the right and left hemispheres was 0.096 and had a p -value of 0.757, meaning there was not a significant difference found between the two ADHD-I groups. When comparing the right hemisphere in ADHD-I versus ADHD-C, the Q -Between was 1.484 with a p -value of 0.223, indicating there is not a significant difference between ADHD-C and ADHD-I in the right hemisphere. When looking at ADHD-C compared to ADHD-I in the left hemisphere, the Q -Between was 0.493 and the p -value was 0.483, meaning there was not a statistical difference between ADHD-I and ADHD-C in the left hemisphere.

Table 4*Results from Subgroup Analyses- Hemisphere*

	Number of effect sizes	Pooled effect size	<i>p</i> -value	<i>Q</i> -Between
ADHD-C Right Hemisphere (RH)	11	-0.308	0.089	
ADHD-C Left Hemisphere (LH)	11	-0.180	0.112	
ADHD-I RH	9	-0.122	0.264	
ADHD-I LH	9	-0.166	0.104	
ADHD-C RH vs. ADHD-C LH			0.840	0.041
ADHD-I RH vs. ADHD-I LH			0.757	0.096
ADHD-C RH vs. ADHD-I RH			0.223	1.484
ADHD-C LH vs. ADHD-I LH			0.483	0.493

When looking at the relations between the subtypes and the volumes of the right and left caudate nucleus, hypothesis 5 was not supported since there were no significant findings (see Table 5). There were 4 effect sizes included for ADHD-C in the right and left caudate nucleus. ADHD-C in the right caudate nucleus had an effect size of -0.139 and a *p*-value of 0.657. ADHD-C in the left caudate nucleus had an effect size of -0.275 and *p*-value of 0.345. There were 3 effect sizes included for ADHD-I in the right and left caudate nucleus. ADHD-I in the right caudate

nucleus had an effect size of 0.191 and p -value of 0.290. ADHD-I in the left caudate nucleus had an effect size of 0.630 and p -value of 0.723.

A further analysis comparing the groups yielded similar results, with no significant findings. When comparing ADHD-C in the right and left caudate nucleus, the Q -Between was 0.240 with a p -value of 0.138. This indicates that there is not a significant difference between the two ADHD-C groups. The Q -Between for ADHD-I in the right and left caudate nucleus was 0.248 and had a p -value of 0.618, meaning there was not a significant difference found between the two ADHD-I groups. When comparing the right caudate nucleus in ADHD-I versus ADHD-C, the Q -Between was 2.201 with a p -value of 0.139, indicating there is not a significant difference between ADHD-C and ADHD-I in the right caudate nucleus. When looking at ADHD-C compared to ADHD-I in the left caudate nucleus, the Q -Between was 1.860 and the p -value was 0.173, meaning there was not a statistical difference between ADHD-I and ADHD-C in the left caudate nucleus. The findings from this analysis can be found in Table 5.

Table 5

Results from Subgroup Analyses- Right Caudate Nucleus (RCN) and Left Caudate Nucleus (LCN)

	Number of effect sizes	Pooled effect size	<i>p</i> -value	<i>Q</i> -Between
ADHD-C RCN	4	-0.139	0.657	
ADHD-C LCN	4	-0.275	0.345	
ADHD-I RCN	3	0.191	0.290	
ADHD-I LCN	3	0.630	0.723	
ADHD-C RCN vs. ADHD-C LCN			0.138	0.240
ADHD-I RCN vs. ADHD-I LCN			0.618	0.248
ADHD-C RCN vs. ADHD-I RCN			0.139	2.201
ADHD-C LCN vs. ADHD-I LCN			0.173	1.860

Publication Bias

Statistical tests were ran to ensure a publication bias did not occur in the current study. An analysis of the funnel plot shown in Figure 5 indicates there is an equal distribution of effect sizes included in the study. Rosenthal's fail-safe was found to be 2855 with a cutoff value of 485. The formula to calculate the cutoff value is: $5 * (\text{number of effect sizes [95]}) + 10$. This indicates that we need

additional 2855 studies with a mean effect size of 0 to have a statistically non-significant pooled effect size. All of these findings indicate there was not (or trivial) a publication bias in the current meta-analysis.

Figure 5

Funnel Plot of Effect Sizes Included in Study

Discussion

A meta-analysis was an appropriate analysis to do on this line of research since there were apparent gaps in prior studies. As previously addressed, whereas some studies had reported a difference in brain volumes across the subtypes, other studies did not find this relationship. Several studies looking at ADHD subtypes had smaller sample sizes. The studies also included mixed information on the subtypes included and brain regions analyzed. In addition to this, there were a limited number of studies in this area of research. Combining the available research strengthened prior findings and tells a better story of the any potential relationship.

The results from this meta-analysis support hypothesis 1, finding a significant decrease in brain volume size in ADHD-C in comparison to controls. This is consistent with prior research reporting significant volume reduction in ADHD-C (Semrud-Clikeman et al., 2017; Carrey et al., 2012). Contrary to the prediction of hypothesis 2, brain volume was not found to be significantly different in ADHD-I; however, it was only slightly above the alpha cutoff (0.05). Volume size in inattentive type being so close to significant could explained by the fact some studies included in this analysis found no difference is volume size in this particular subtype, whereas other studies did (Al-Amin et al., 2018, Vilgis et al., 2016; Semrud-Clikeman et al., 2017).

The findings support hypothesis 3 in predicting that there would be a significant decrease in brain volume size in males when compared to females.

When we consider the gender (% of male) as a moderator, we found significant negative effectiveness indicating a larger proportion of males in the sample have a significant decrease in volume size. This is consistent with prior research that found significant reductions in boys compared to girls (Villemonteix et al., 2015). There is a higher prevalence of ADHD-C in males, and as our results show, there is a significant brain volume reduction in combined type (Wang et al., 2018).

The analyses on the right and left regions were done since prior studies have reported changes in structures in the specific hemispheres (Vilgis et al., 2016; Pineda et al, 2002; Farmer, 2001). Since there were so many structures and regions reported in the studies, it was challenging to group areas together in a meaningful way for further analysis; therefore, if the structure was specified as being in the right or left side, it was grouped together. Hypothesis 4 had predicted a difference in the hemispheres, but the findings from the subgroup analysis did not support this. There were no clear relations between the volumes in ADHD-C and ADHD-I when looking at the right and left hemisphere. This finding was unexpected since a number of studies have reported significant findings. This could be explained by current study's loose grouping of regions.

The analysis on the caudate nucleus was done since prior studies have examined this structure and it was the most frequent region reported in the current meta-analysis. There have been inconsistent findings on this region, so it was important to better understand what is occurring. Semrud-Clikeman et al. (2017)

reported that children with combined type have bilaterally smaller volumes in the caudate nucleus. Pineda et al. (2002) found that the left caudate nucleus head volume was significantly larger in the left side compared to the right in both ADHD-C and ADHD-I. Carrey et al. (2012) found that the caudate nucleus in combined type is smaller, but when controlling for age, the difference only prevailed in the group of participants in the 5.9-7.3 year range. Vilgis et al. (2016) had similar findings that support age as being a predictor of volume size in the right caudate nucleus, with younger age being associated with smaller volume sizes in this structure. The analyses looked at differences in the left and right regions and between the two subtypes, and no significant relations were found. Although hypothesis 5 predicted there would be a change in this region, the current findings are not in support of prior research that found a significant volume reduction or changes in the caudate nucleus.

A component that is missing from the current study is an analysis on racial and ethnic differences in the ADHD subtypes. In the 8 studies included, 6 did not report any information on the race or ethnicity of participants. The seventh study vaguely reported that twenty percent of participants were self-declared minorities, with no further information (Semrud-Clikeman et al., 2017). The eighth study specified it was done in China; however, drawing a conclusion based on that piece of information would be inaccurate (Sun et al., 2018). Since minorities account for a large percentage of the population in the United States, it is important to

understand if these findings are generalizable across the various demographic groups.

Implications

The inclusion of an ADHD specifier for subtype is the current DSM-5 diagnostic criteria. With rates of this ADHD being so high, it is crucial to research and better understand components of this disorder to make sure it is truly valid on all levels. The findings in the current study show that there are differences across the subtypes since there are a number of significant findings consistent with the majority of prior research.

The findings support the current diagnostic measures on a neuroanatomical level, more strongly with ADHD-C. Although ADHD-I was slightly insignificant, there are apparent differences in brain volumes that occur in the two subtypes. There is also strong support that the two subtypes are separate entities and should continue to be recognized as such.

Knowing more about this disorder has the potential to help in a number of ways. This method could help as an additional diagnostic or assessment measure. In addition, since this disorder has been shown to manifest in several variations, knowing more about the brain regions affected in the subtypes could help develop more individualistic treatment in individuals.

Limitations

There were some identified limitations in this study. There is not a consistent protocol of how brain volumes were obtained. It is hard to determine accuracy of methods of obtaining the volumes and if there is reliability across the studies. Prior studies looked at individual structures or regions of the brain. Since there is a scarcity in this area of research, studies were not excluded based on brain regions studied. Due to vast differences in structures reported in the studies included in this analysis, it was difficult to categorize the regions in a meaningful way that could be analyzed. It is hard to predict what regions accounted for the findings since the subgroup analysis did not yield significant findings. This could also be due to the limited number of effect sizes in these regions.

Another limitation is that there was a skew in populations studied and reported findings. Two of the studies included only reported on hyperactive type. Although a small number of effect sizes came from these studies, it still created a difference in the sample. Another concern with the sample is that a high proportion of participants in the studies were male. Some of the studies used in this analysis only included male participants. The current diagnostic criterion for ADHD has a specifier for level of severity. Studies did not report the severity of participants included. Since this disorder does manifest in a spectrum-like fashion, it is hard to rule out if the level of severity contributed to the findings.

Background and demographic information were not included for analysis due to insufficient information. In the case of age, the data could not be used since numerous studies reported overall information for the sample rather than specific to the groups within the study. Due to this, age is a major limitation since a few studies included in this analysis reported structural differences dependent on the age of the participants (Vilgis et al., 2016; Carrey et al., 2012). Another major limitation is that there is no data on racial or ethnic backgrounds of the participants in any of the studies included. This makes it extremely difficult to generalize since there is no way of knowing if the sample is truly representative of the population.

Future Direction

Although the findings are important, this area of research should further be expanded on. Future research should aim at narrowing down groups by age. As discussed, due to insufficient reporting of ages within groups in the studies, this variable could not be analyzed. Studies have reported that structural differences are related to the age of the individual; therefore, this is important to analyze in such ways as a meta-analysis to determine if this relation is still present when combining findings (Vilgis et al., 2016; Carrey et al., 2012). This analysis will tell more about the strength of prior findings and give a better idea of when in development any potential structural differences occur.

In addition, researchers should seek to further categorize brain regions. There are significant differences overall in volume size dependent on subtype, but

this study did not uncover what regions accounted for these relations. There was a large number of regions reported in the studies, which made it difficult to create groupings that would make sense based on function. A better grouping system will hopefully help to uncover which regions or structures contribute to some of the significant differences found.

References

- Abikoff, H.B., Jensen, P.S., Arnold, L.L.E., Hoza, B., Hechtman, L., Pollack, S., Martin, D., Alvir, J., March, J.S., Hinshaw, S., Vitiello, B., Newcorn, J., Greiner, A., Cantwell, D.P., Conners, C.K., Elliot, G., Greenhill, L.L., Kraemer, H., Pelham Jr., W.E., Severe, J.B., Swanson, J.M., Wells, K., & Wigal, T. (2002). Observed classroom behavior of children with ADHD: Relationship to gender and comorbidity. *Journal of Abnormal Child Psychology*, 30, 349– 359. <https://doi.org/10.1023/A:1015713807297>
- Al-Amin, M., Zinchenko, A., & Geyer, T. (2018). Hippocampal subfield volume changes in subtypes of attention deficit hyperactivity disorder. *Brain Research*, 1685. <https://doi.org/10.1016/j.brainres.2018.02.007>
- American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.
- Arnold, L.E., Hodgkins, P., Kahle, J., Madhoo, M., & Kewley, G. (2015). Long-term outcomes of ADHD: academic achievement and performance. *Journal of Attention Disorders*. <https://doi.org/10.1177/1087054714566076>
- August, G.J., Realmuto, G.M., MacDonald III, A.W., Nugent, S.M., & Crosby, R. (1996). Prevalence of ADHD and comorbid disorders among elementary school children screened for disruptive behavior. *Journal of Abnormal Child Psychology*, 24, 571-595. <https://doi.org/10.1007/BF01670101>

- Biederman, J., Fried, R., Petty, C., Mahoney, L., & Faraone, S.V. (2012). An examination of the impact of attention-deficit hyperactivity disorder on IQ: a large controlled family-based approach. *The Canadian Journal of Psychiatry*, 257, 608-616. <https://doi.org/10.1177/070674371205701005>
- Biederman, J., Makris, N., Valera, E.M., & Monuteaux (2008). Towards further understanding of the co-morbidity between attention deficit hyperactivity disorder and bipolar disorder: a study of brain volumes. *Psychological Medicine*, 38(7). <https://doi.org/10.1017/S0033291707001791>
- Bledsoe, J., Semrud-Clikeman, M., & Pliszka, S.R. (2009). A magnetic resonance imaging study of the cerebellar vermis in chronically treated and treatment-naïve children with attention-deficit/hyperactivity disorder combined type. *Biological Psychiatry*, 65, 620-624.
[doi:10.1016/j.biopsych.2008.11.030](https://doi.org/10.1016/j.biopsych.2008.11.030)
- Borger, N. & Meere, J.V.D. (2000). Motor control and state regulation in children with ADHD: a cardiac response study. *Biological Psychology*, 51.
[https://doi.org/10.1016/S0301-0511\(99\)00040-X](https://doi.org/10.1016/S0301-0511(99)00040-X)
- Brown, T.E. (2002). DSM-IV: ADHD and executive function impairment. *Advanced Studies in Medicine*, 2(25). Retrieved from:
https://www.researchgate.net/profile/Thomas_Brown14/publication/242730401_DSMIV_ADHD_and_executive_function_impairments/links/02e7e52fed469a995e000000.pdf

Bussing, R. & Gary, F.A. (2001). Practice guidelines and parent ADHD treatment evaluations: Friends of foes? *Harvard Review of Psychiatry*, 9.

doi: 10.1080/10673220127905

Bussing, R., Grudnik, J., Mason, D., Wasiak, M., & Leonard, C. (2002). ADHD and conduct disorder: An MRI study in a community sample. *The World Journal of Biological Psychiatry*, 3.

<https://doi.org/10.3109/15622970209150624>

Carlson, C.L., Tamm, L., & Gaub, M. (1997). Gender differences in children with ADHD, ODD, and co-occurring ADHD/ODD identified in a school population. *Journal of the American Academy of Child & Adolescent Psychiatry*, 36 (12).

<https://doi.org/10.1097/00004583-199712000-00019>

Carrey, M., Bernier, D., Emms, M., Gunde, E., Sparkes, S., MacMaster, F.P., & Rusak, B. (2012). Smaller volume of caudate nuclei in prepubertal children with ADHD: Impact of age. *Journal of Psychiatric Research*, 46.

doi:10.1016/j.jpsychires.2012.04.025

Castellanos, F.X., Lee, P.P., & Sharp, W. (2002). Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. *JAMA*, 288(14).

doi:10.1001/jama.288.14.1740

Centre for Neuro Skills (n.d.). Frontal lobes. Retrieved from:

<https://www.neuroskills.com/brain-injury/frontal-lobes/>

- Chaudry, A., Jackson, A., & Glied, S.A. (2019). Did the affordable care act reduce racial and ethnic disparities in health insurance coverage? *The Commonwealth Fund*. Retrieved October 8, 2020, from https://www.commonwealthfund.org/sites/default/files/2020-02/Chaudry_did_ACA_reduce_racial_disparities_ib_v4.pdf
- Children and Adults with Attention-Deficit/Hyperactivity Disorder (n.d.). General Prevalence of ADHD. Retrieved from: <https://chadd.org/about-adhd/general-prevalence/>
- Cherry, K. (2019). Hippocampus role in the limbic system. Retrieved from: <https://www.verywellmind.com/what-is-the-hippocampus-2795231>
- Cooper, H., Hedges, L.V., & Valentine, J.C. (2009). *The handbook of research synthesis and meta-analysis* (2nd ed.). New York: NY: Russel Sage Foundation.
- Elia, J., Ambrosini, P. & Berrettini, W. (2008). ADHD characteristics: I. Concurrent co-morbidity patterns in children & adolescents. *Child and Adolescent Psychiatry Mental Health, 1*. <https://doi.org/10.1186/1753-2000-2-15>
- Farmer, L.J. (2002). A comparison between children with inattentive and combined subtypes of ADHD using neuropsychological and neuroanatomical measures (Doctoral dissertation). *Available from ProQuest*. UMI: 3072033.
- Fisher, Z. & Tipton, E. (2015). Robumeta: An R-package for robust variance

estimation in meta-analysis. *ResearchGate*. Retrieved from:

https://www.researchgate.net/publication/273388328_robustmeta_An_R-package_for_robust_variance_estimation_in_meta-analysis

Glass, G. (1976). Primary, Secondary, and Meta-Analysis of Research. *Educational Researcher*, 5(10), 3-8. Retrieved from:

<http://www.jstor.org/stable/1174772>

Gogolla, N. (2017). The insular cortex. *Current Biology*, 27.

<https://doi.org/10.1016/j.cub.2017.05.010>

Graetz, B.W., Sawyer, M.G., & Baghurst, P. (2005). Gender differences among children with DSM-IV ADHD in australia. *Child and Adolescent Psychiatry*, 44.

<https://doi.org/10.1097/00004583-200502000-00008>

Heathline (2015). Caudate nucleus. Retrieved from:

<https://www.healthline.com/human-body-maps/caudate-nucleus#1>

Huang, Y., Zheng, S., Xu, C., Lin, K., Wu, K., Zheng, M., Zhang, J., & Xu, H.

(2017). Attention-deficit hyperactivity disorder in elementary school students in Shantou, China: prevalence, subtypes, and influencing factors.

Neuropsychiatric Disease and Treatment, 13. doi: 10.2147/NDT.S126100

Jarratt, K.P., Riccio, C.A., & Siekierski, B.M. (2005). Assessment of attention

deficit hyperactivity disorder (ADHD) using the BASC and BRIEF. *Applied*

Neuropsychology, 12(2). https://doi.org/10.1207/s15324826an1202_4

- Kaiser, M.L., Schoemaker, M.M., Albaret, J.M., & Geuze, R.H. (2015). What is the evidence of impaired motor skills and motor control among children with attention deficit hyperactivity disorder (ADHD)? Systematic review of the literature. *Research in Developmental Disabilities, 36*.
<https://doi.org/10.1016/j.ridd.2014.09.023>
- Lockwood, K.A., Marcotte, A.C. & Stern, C. (2001). Differentiation of attention-deficit/hyperactivity disorder subtypes: Application of a neuropsychological model of attention. *Journal of Clinical and Experimental Neuropsychology, 23*(1). doi: 10.1076/jcen.23.3.317.1179
- Mayes, S.D., Calhoun, S., Bixler, E.D., & Vgontzas, A.N. (2009). Sleep problems in children with autism, ADHD, anxiety, depression, acquired brain injury, and typical development. *Sleep Medicine Clinics, 4*(1).
<https://doi.org/10.1016/j.jsmc.2008.12.004>
- Mayo Clinic (n.d.). MRI overview. Retrieved from:
<https://www.mayoclinic.org/tests-procedures/mri/about/pac-20384768>
- Morgan, P.L., Hillemeier, M.H., Farkas, G., & Maczuga, S. (2014). Racial/ethnic disparities in ADHD diagnosis by kindergarten entry. *The Journal of Child Psychology and Psychiatry, 55*(8). <https://doi.org/10.1111/jcpp.12204>
- Morgan, P.L., Staff, J., Hillemeier, M.H., Farkas, G., & Maczuga, S. (2013). Racial and ethnic disparities in ADHD diagnosis from kindergarten to eighth grade. *Pediatrics, 132*(1). <https://doi.org/10.1542/peds.2012-2390>

Neuroscientifically Challenged (n.d.). Anterior cingulate cortex. Retrieved from:

<https://www.neuroscientificallychallenged.com/glossary/anterior-cingulate-cortex>

Neuroscientifically Challenged (2015). Know your brain: Default mode network.

Retrieved from: <https://www.neuroscientificallychallenged.com/blog/know-your-brain-default-mode-network>

Newcorn, J.H., Halperin, J.M., Jensen, P.S., Abikoff, H.B., Arnold, E., Cantwell,

D.P., Conners, C.K., Elliot, G.R., Epstein, J.N., Greenhill, L.L., Hechtman, L., Hinshaw, S.P., Hoza, B., Kraemer, H.C., Pelham, W.E., Severe, J.B.,

Swanson, J.M., Wells, K.C., Wigal, T., & Vitiello, B. (2001). Symptom profiles in children with ADHD: Effects of comorbidity and gender.

Journal of the American Academy of Child & Adolescent Psychiatry, 20(2), 137-146. <https://doi.org/10.1097/00004583-200102000-00008>

Pineda, D.A., Restrepo, M.A., Sarmiento, R.J., Gutierrez, J.E., Vargas, S.A.,

Quiroz, Y.T., & Hynd, G.W. (2002). Statistical analyses of structural magnetic resonance imaging of the head of the children with attention-deficit hyperactivity disorder. *Journal of Child Neurology*, 17(2).

<https://doi.org/10.1177/088307380201700202>

Qureshi, M.N.I., Min, B., Jo, H.J., & Lee, B. (2016). Multiclass classification from the differential diagnosis on the ADHD subtypes using recursive feature

elimination and hierarchical extreme learning machine: structural MRI study. *PLOS ONE*. doi:10.1371/journal.pone.0160697

Rosch, K.S., Crocetti, D., Hirabayashi, K., Denckla, M.B., Mostofsky, S.H., & Mahone, E.M. (2018). Reduced subcortical volumes among preschool-age girls and boys with ADHD. *Psychiatry Research: Neuroimaging*, 271. <https://doi.org/10.1016/j.psychresns.2017.10.013>

Semrud-Clikeman, M., Fine, J.G., Bledsoe, J., & Zhu, D.C. (2017). Regional volumetric differences based on structural MRI in children with two subtypes of ADHD and controls. *Journal of Attention Disorders*, 21(12). <https://doi.org/10.1177/1087054714559642>

Semrud-Clikeman, M., Pliszka, S.R., Lancaster, J., & Liotti, M. (2006). Volumetric MRI differences in treatment-naïve vs chronically treated children with ADHD. *Neurology*, 67. <https://doi.org/10.1212/01.wnl.0000237385.84037.3c>

Stein, M.A. (1999). Unravelling sleep problems in treated and untreated children with ADHD. *Journal of Child and Adolescent Psychopharmacology*, 9(2). <https://doi.org/10.1089/cap.1999.9.157>

Subcommittee on Attention-Deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement and Management, Wolraich, M., Brown, L., Brown, R. T., DuPaul, G., Earls, M., Feldman, H. M., Ganiats, T. G., Kaplanek, B., Meyer, B., Perrin, J., Pierce, K., Reiff, M., Stein, M. T., &

Visser, S. (2011). ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics*, 128(5), 1007–1022.

<https://doi.org/10.1542/peds.2011-2654>

Sun, H., Chen, Y., Huang, Q., Lui, S., Shi, Y., Xu, X., Sweeney, J.A., & Gong, Q. (2018). Psychoradiologic Utility of MR Imaging for Diagnosis of Attention Deficit Hyperactivity Disorder: A Radiomics Analysis. *Radiology*, 287(2). doi: 10.1148/radiol.2017170226

The Human Memory (2019a). Gray and white matter: Structures and function.

Retrieved from: <https://human-memory.net/gray-white-matter/>

The Human Memory (2019b). Parietal lobe and its function. Retrieved from:

<https://human-memory.net/parietal-lobe/>

The Human Memory (2019c). Temporal brain lobe. Retrieved from:

<https://human-memory.net/temporal-brain-lobe/>

Viechtbauer, W. (2010). Conducting meta-analyses in R with the metafor package.

Journal of Statistical Software, 36(3), 1-48. doi:10.18637/jss.v036.i03

Vilgis, V., Sun, L., Chen, J., Silk, T.J., & Vance, A. (2016). Global and local grey matter reductions in boys with ADHD combined type and ADHD

inattentive type. *Psychiatry Research: Neuroimaging*, 254.

<http://dx.doi.org/10.1016/j.psychresns.2016.06.008>

- Villemonteix, T., De Brito, S.A., Slama, H., Kavec, M., Baleriaux, D., Metens, T., Bajjot, S., Mary, A., Peigneux, P., & Massat, I. (2015). Grey matter volume differences associated with gender in children with attention-deficit/hyperactivity disorder: A voxel-based morphometry study. *Developmental Cognitive Neuroscience, 14*.
<https://doi.org/10.1016/j.dcn.2015.06.001>
- Wang, Y., Xu, Q., Li, S., Li, G., Zuo, C., Liao, S., Long, Y., Li, S., & Joshi, R.M. (2018). Gender differences in anomalous subcortical morphology for children with ADHD. *Neuroscience Letters, 665*(5).
<https://doi.org/10.1016/j.neulet.2017.12.006>
- Webster-Stratton, C.H., Reid, M.J., & Beauchaine, T. (2011). Combining parent and child training for young children with ADHD. *Journal of Clinical Child & Adolescent Psychology, 40*(2).
<https://doi.org/10.1080/15374416.2011.546044>
- Wigal, T., Greenhill, L., Chuang, S., McGough, J., Vitiello, B., Skrobala, A., Swanson, J., Wigal, S., Abikoff, H., Kollins, S., McCracken, J., Riddle, M., Posner, K., Ghuman, J., Davies, M., Thorp, B., & Stehli, A. (2006). Safety and tolerability of methylphenidate in preschool children with ADHD. *Journal of the American Academy of Children & Adolescent Psychiatry, 45*(11). <https://doi.org/10.1097/01.chi.0000235082.63156.27>

Wilens, T., MCBurnett, K., Stein, M., Lerner, M., Spencer, T., & Wolraich, M.

(2005). ADHD treatment with once-daily OROS methylphenidate: Final results from a long-term open-label study. *Journal of the American Academy of Children & Adolescent Psychiatry*, 44(10).

<https://doi.org/10.1097/01.chi.0000173291.28688.e7>

Willcut, E.G., Nigg, J.T., Pennington, B.F., Solanto, M.V., Rohde, L.A., Tannock,

R., Loo, S.K., Carlson, C.L., MCBurnett, K., & Lahey, B.B. (2012). Validity of DSM-IV attention deficit/hyperactivity disorder symptom dimensions and subtypes. *Journal of Abnormal Psychology*, 121(4).

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Appendix A*Sample Characteristics of Studies Included in Meta-Analysis*

Author	Year published	Total Sample	ADHD-C sample	ADHD-I sample	Number of effect sizes	Proportion of ADHD-C males	Proportion of ADHD-I males
Al-Amin et al.	2018	880	197	131	24	0.81	0.73
Pineda et al.	2002	45	15	15	4	0.47	0.47
Blesdoe et al.	2009	47	14	0	5	0.68	NA
Carrey et al.	2012	50	26	0	4	1	NA
Semrud-Clikeman et al.	2017	74	25	22	18	0.88	0.86
Sun et al.	2018	83	43	40	8	0.86	0.85
Vilgis et al.	2016	79	33	15	8	1	1
Farmer	2002	54	15	14	24	0.73	0.71