Degree project

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Gray Matter Volume in Medication-Naïve Individuals with ADHD: A Systematic Review of Voxel-Based Morphometry MRI-studies

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Abstract

Attention deficit hyperactivity disorder is one of the most common neurodevelopmental disorders, affecting around 7% of the worldwide population in their everyday life. It has been suggested that individuals with ADHD differ in gray matter volume from typically developing controls. However, findings on in which brain areas these differences are located, as well as how gray matter volume is affected by stimulant medication, remain inconclusive. Therefore, this systematic review aimed to investigate any potential differences in gray matter volume in medication-naïve individuals with ADHD compared to controls, focusing on studies using voxel-based morphometry applied to MRI-imaging data A keyword search in the databases Web of Science, Scopus and Medline EBSCO resulted in 349 studies, of which seven met the inclusion criteria and were included in the review. The results included a total of 169 participants diagnosed with ADHD and 148 typically developing controls. Findings suggested decreased cerebellar gray matter volume, potential gender-wise volume differences in the anterior cingulate cortex, and a decrease in caudate gray matter volume, specifically in adults with ADHD. Some limitations include small sample sizes, possible effects of age on gray matter volume, and the overall heterogeneous nature of the disorder. The present review agrees that individuals with ADHD exhibit differences in gray matter volume, but also highlights the importance of expanding research on medication-naïve subjects, to be able to draw more robust scientific conclusions about the neural correlates of ADHD in the future.

Keywords: attention deficit hyperactivity-disorder, gray matter, medication-naïve, structural magnetic resonance imaging, voxel-based morphometry

Gray Matter Volume in Medication-Naïve Individuals with ADHD: A Systematic Review of Voxel-Based Morphometry MRI-studies

Attention Deficit Hyperactivity Disorder

Attention deficit hyperactivity disorder (ADHD) has, in recent years, become a popular topic of research in the scientific community. It is one of the most common neurodevelopmental disorders, especially in children and adolescents, with a prevalence of around 7% of the population globally (Rubia, 2018; Sutcubasi Kaya et al., 2016). ADHD is diagnosed in children and adolescents if they meet the criteria of at least six symptoms of inattention or hyperactivity/impulsivity, if these symptoms are inappropriate age-wise, and have persisted for over six months (American Psychiatric Association, 2013). One must also have displayed ADHD symptoms before the age of 12. Adults with ADHD need only exhibit five symptoms to meet the criteria for diagnosis. In the majority of cases where ADHD was diagnosed in childhood, the psychiatric condition persists into adulthood (Nakao et al., 2011). Direct causes of ADHD are unknown, but underlying factors are seemingly both genetic and environmental and result in a variety of cognitive impairments, such as inattentiveness, poor impulse inhibition, mood dysregulation and overall executive dysfunction (Yu et al., 2023). Because of this, ADHD impairs social, academic and workplace factors in affected individuals (Kumar et al., 2017). ADHD also presents very heterogeneously and is often found comorbid with other psychiatric disorders, such as oppositional defiant disorder, conduct disorder and anxiety disorders, making it challenging to treat and draw empirical conclusions (Schweren et al., 2013).

Mechanism of ADHD

A review by Luo et al. (2019) summarizes some of the models that have attempted to explain the underlying mechanisms of ADHD. One category of models is concerned with the impairments of cognitive functions and motivation often seen in the disorder. For example, Barkley (1997) suggested that symptoms of impulsivity and hyperactivity could be explained by an impairment in behavioral inhibition, resulting in executive dysfunction in areas such as

working memory, planning and affect regulation. Connecting this to neurobiological theory, the fronto-striatal circuit has been suggested as a neural correlate of ADHD (Bush et al., 2005). Functional magnetic resonance imaging (fMRI) studies have associated enhanced functional connectivity between the frontal cortex and the striatum with better performance in tasks involving response inhibition, as well as working memory. However, this line of explanation does not really explain the connection to inattentive symptoms (Luo et al., 2019).

The Cognitive-Energetic Model, formed by Sergeant (2000), focuses on how cognition interplays with arousal, as well as executive functioning. This model suggests that deficits in performance displayed by individuals with ADHD in cognitive tasks are due to conditions being suboptimal for the level of arousal and activation of the participant. This means that adjusting aspects like speed of stimulus presentation, or implementing external rewards to increase motivation, could result in performance closer to that of typically developing controls (Luo et al., 2019).

Lastly, there is also the neurodevelopmental perspective, focusing on structural and functional abnormalities in the brain of ADHD patients. Halperin and Schultz (2006) suggested that ADHD is characterized by deficits in the brainstem and thalamus, and that symptoms would decrease with the development of the prefrontal cortex (Luo et al., 2019). Shaw et al. (2007) found that children with ADHD compared to controls reached peak cortical thickness at a later stage, leading to a theory of delayed cortical maturation. This delay in maturation has been suggested to not only involve the prefrontal cortex, but also brain areas like the anterior cingulate cortex and cerebellum (Luo et al., 2019).

Gray Matter Volume in ADHD

Searching for potential biomarkers in the form of structural brain abnormalities, compared to typically developing individuals through neuroimaging, could help evaluate and strengthen some of the previously mentioned models. Therefore, this review will focus specifically on measures of gray matter volume. Recent magnetic resonance imaging (MRI) studies seem to agree that ADHD has been associated with differences in brain structure

compared to typically developing controls (TDCs) (Nakao et al., 2011; Yu et al., 2023). Several studies have concluded that individuals with ADHD exhibit a reduction in total gray matter volume (GMV) across the brain (Nakao et al., 2011; Sáenz et al., 2020). Regionally speaking, findings have been rather inconclusive, with reports of the localization of this decrease in GMV being rather varied. Some brain regions that recurrently are reported to have reduced gray matter volume in ADHD samples include the prefrontal/frontal cortex, the corpus callosum, the basal ganglia, and the cerebellum (Kumar et al., 2017; Montes et al., 2010; Sáenz et al., 2020; Villemonteix et al., 2015b). However, these findings are sometimes contradictory across studies.

For example, a meta-analysis of 14 studies by Nakao et al. (2011) found that individuals with ADHD had significantly lower GMV, both in a global and regional sense. A cluster encompassing the lentiform nucleus and the caudate nucleus consistently presented with smaller GMV compared to TDCs. These areas within the basal ganglia are involved in systems responsible for executive functions like attention and inhibition, commonly impaired in the disorder. They also found that in the left posterior cingulate cortex, individuals with ADHD actually displayed larger gray matter volume than controls. A more recent meta-analysis of 29 MRI-studies by Yu et al. (2023) found regional differences in GMV in participants with ADHD, including decreases in the corpus callosum, the limbic system and frontoparietal regions. Conversely to Nakao et al. (2011), they found increases of GMV, rather than decreases, in the left lentiform and right caudate nucleus.

Pharmacological Treatment

A factor that could add to the heterogeneous nature of the findings on gray matter volume in ADHD is the fact that the neurodevelopmental disorder is commonly treated with stimulant medication. Amphetamines (in the form of, for example, Adderall or Dextrostat) and, more frequently, methylphenidate (in the form of Ritalin, Concerta, etc.) are used for their dopamine-enhancing properties (Luo et al., 2019).

A relatively small number of studies have investigated the effects of pharmacological ADHD-treatment on GMV over time. Some suggest that the gray matter volume of medicated participants is more normalized compared to medication-naïve ones. For example, Nakao et al. (2011) found that the use of stimulant medication in individuals with ADHD was associated with more normalized gray matter volume of the basal ganglia. A review by Schweren et al. (2013) also reported that both medicated and medication-naïve children with ADHD showed decreases in GMV, but that regional normalization in the anterior cingulate cortex, thalamus and cerebellum correlated with stimulant medication.

Despite the possibility of pharmacological treatment affecting brain structure, it is not common to study completely medication-naïve samples. The majority of research uses samples consisting of a mix of medicated, previously medicated and never medicated participants. Some require a "wash-out" of refraining from medication for a certain amount of time before study procedures (see for example Lim et al., 2014). However, these wash-outs can range from 24 hours to a week, and perhaps affect results functionally, but should not have an immediate effect on brain structure such as gray matter. To ensure that MRI GMV-findings are in fact related to ADHD and not confounded by psychotropic medication use, it is important to conduct and compile research on medication-naïve populations.

Aim

The aim of this review is to compile reports about the structural neural correlates of ADHD, attempting to remove aspects that can contribute to the heterogeneity of findings in structural neuroimaging studies on ADHD populations. To do this, the review will focus on medication-naïve participants, as well as a homogeneous way of analyzing MRI-images. The technique that has been chosen is voxel-based morphometry (VBM), which uses standardized templates to compare voxel-wise differences in GMV. The present review will investigate what differences in gray matter volume recent studies utilizing voxel-based morphometry have found between a medication-naïve ADHD population and typically developing controls.

Methods

Search Strategy

Studies were identified on February 23, 2024, through keyword searches in three databases: Web of Science, Scopus and Medline EBSCO. The keywords utilized were: (adhd OR "attention deficit hyperactivity disorder") AND (vbm OR "voxel based morphometry") AND ("gray matter" OR "grey matter"). The same search string was used in each database, with no filters applied, to avoid differing conditions in search results across databases. The results were uploaded to the review software tool Rayyan, which was used in identifying and removing duplicates and recording the screening process (Ouzzani et al., 2016). Articles were scrutinized by a single reviewer (the author). In the initial stage, studies were screened based on title and abstract, being excluded if they were non-experimental studies; such as review articles, meta-analyses, book chapters or conference abstracts. Articles were also excluded if they were apparently irrelevant to the research question, for example, if they did not contain mention of ADHD or MRI. The remaining studies were assessed for eligibility through full text screening.

The database search resulted in a total of 349 records. Out of these, 170 were identified as duplicates, which after removal left 179 records to be screened. During screening n=115 irrelevant records were excluded, meaning n=64 articles were assessed for eligibility, amongst them n=1 could not be retrieved in full text. Ultimately seven studies were found, investigating gray matter volume through VBM, comparing medication-naïve ADHD individuals to typically developing controls (see Figure 1).

Inclusion & Exclusion Criteria

The aim of the review was to investigate differences in gray matter volume between medication-naïve ADHD individuals, as classified by the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013), and typically developing individuals, using voxel-based morphometry (VBM) analysis. Studies were included if they 1) were experimental studies published in peer-reviewed journals, 2) were published in English,

3) were ethically approved by an institutional review board or ethics committee, 4) used participants diagnosed with attention deficit-hyperactivity disorder assessed by DSM criteria, 5) used control groups consisting of typically developing individuals, 6) used structural magnetic resonance imaging (MRI), 7) measured gray matter volume using voxel-based morphometry (VBM), and 8) used ADHD individuals who had never received pharmacological treatment for the neurodevelopmental disorder, meaning participants had to be medication-naïve.

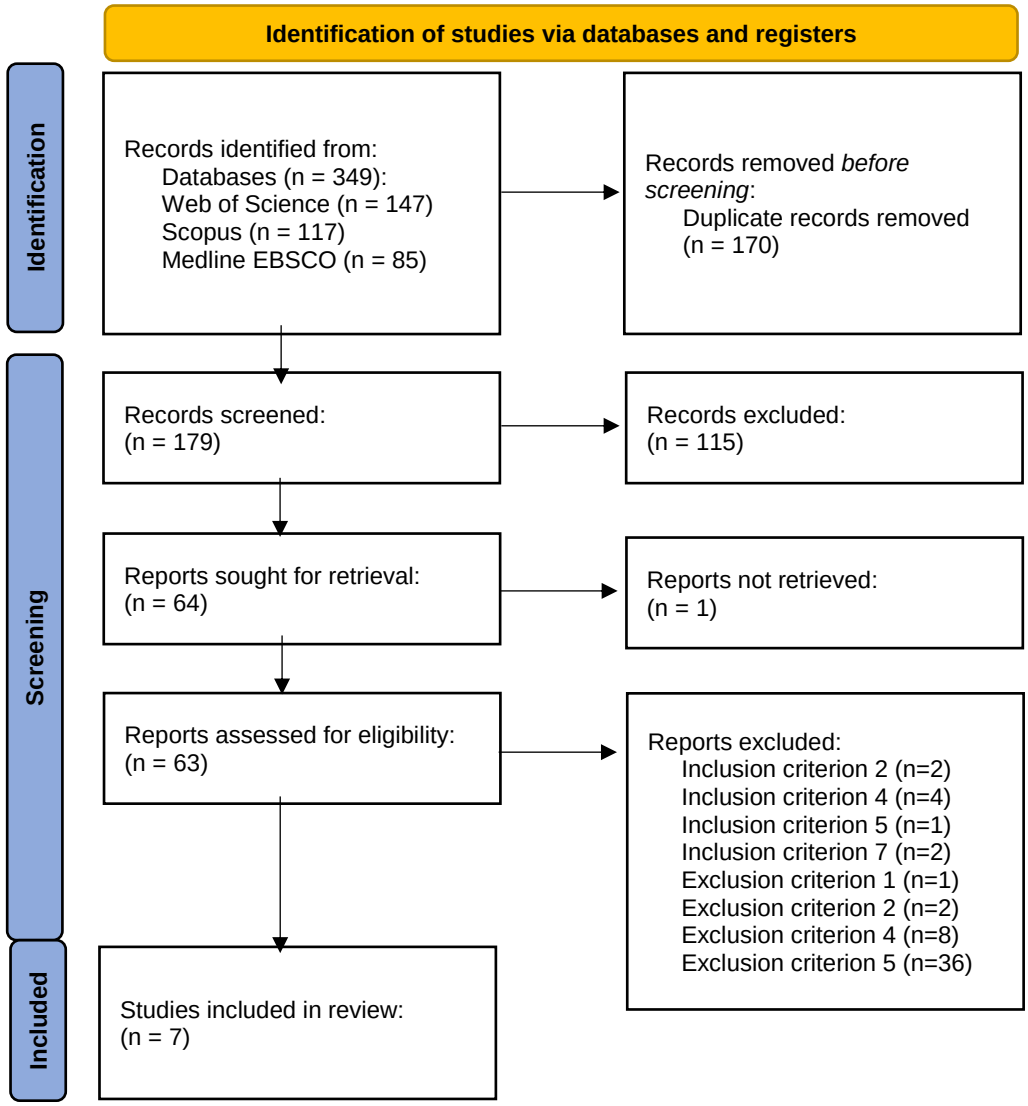
Studies were excluded if they 1) focused on samples where ADHD was comorbid with another psychiatric disorder, 2) did not include a measure of gray matter volume (e.g., only measured gray matter density, cortical thickness or total intracranial volume), 3) compared an ADHD group to a group with another psychiatric disorder, but not to typically developing controls, 4) did not statistically compare an ADHD group and a typically developing group on gray matter volume, and 5) used participants that were not fully medication-naïve, for example, if they had only temporarily refrained from medication prior to experimental procedures, or if the study only used partially medication-naïve participants.

Data Extraction

The following data was extracted from the final included articles: title, authors, year of publication, sample size (ADHD and control groups separated), gender distribution, age mean and standard deviation, statistical testing, VBM application, regions of interest and key findings.

Figure 1

PRISMA Flow Chart



Note: Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T., Mulrow, C. D., Shamseer, L., Tetzlaff, J., Akl, E. A., Brennan, S., Chou, R., Glanville, J., Grimshaw, J., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E., Mayo-Wilson, E., McDonald, S., . . . Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*, n71. https://doi.org/10.1136/bmj.n71

Results

In total, the final seven studies included 169 participants diagnosed with ADHD and 148 typically developing controls, with sample sizes ranging from 36 to 60 participants. Across studies, 64% of ADHD individuals and 62% of TDCs were male. One of the studies included only male participants (Kumar et al., 2017). Participant ages ranged from 7 to 59 years, with the majority (n=5) of studies involving pediatric samples around the mean age of 10. Regarding the diagnosis of ADHD, six studies used diagnostic criteria from the 4th edition of DSM, two of which used the text revision version. One study used the 5th edition. All seven studies used comparison groups of typically developing controls, but two studies used an additional comparison group, with the first being a medicated ADHD group (Villemonteix et al., 2015a), and the second being individuals with autism spectrum disorder (Sáenz et al., 2020). Statistical comparisons with these groups were not included in the review. Regarding image acquisition, the majority of the studies (n=4) used a 3T MRI scanner, two used a 1.5T one, and the last one a 1T scanner. A summary of the data extracted from each study can be found in Table 1.

Montes et al. (2010) compared the GMV of the right caudate in 20 adults aged 25-35 with ADHD with an age- and gender-matched control group of TDCs. Reductions in this area had been previously found in ADHD children, but negative findings had also been reported. Therefore, they investigated which was the case in an adult sample. Additionally, they conducted a gender-wise comparison across the groups. The GMV of part of the right caudate nucleus showed a decrease in volume compared to controls. The findings were the same in both male and female comparisons to typically developing controls.

Makris et al. (2013) also studied an adult sample, the GMV of 24 ADHD individuals between the ages of 18 and 59 was compared to age- and gender-matched controls. Based on previous findings, they established six regions of interest (ROIs): the dorsolateral prefrontal cortex (DLPFC), the anterior cingulate cortex (ACC), the orbitofrontal cortex (OFC), the lateral parieto-temporal cortex (more specifically the inferior parietal lobule/temporo-

occipito-parietal region, IPL/TOP), the caudate nucleus, and the cerebellum. They hypothesized that medication-naïve ADHD adults would showcase structural differences compared to controls in these regions. The results indicated that ADHD adults had increased GMV in parts of the OFC, IPL/TOP and DLPFC, while they exhibited decreased GMV in parts of the caudate nucleus, cerebellum and ACC. After correcting for multiple comparisons, the decrease in cerebellum GMV was the only significant difference remaining.

Villemonteix et al. (2015a) investigated a pediatric sample of children aged 7.3 to 12.9 years. Thirty-three were medication-naïve with ADHD, and 24 were typically developing controls. This study also included a group of 20 ADHD children with a history of stimulant treatment. They explored differences in GMV conducting both whole brain and ROI analyses, using the bilateral caudate nucleus, amygdala and nucleus accumbens as a priori ROIs. These regions of interest resulted in no significant differences across the groups, but when comparing medication-naïve ADHD children to TDCs, decreases in GMV were found in the insula and in the middle temporal lobe.

Villemonteix et al. (2015b) seemingly used the same ADHD group as Villemonteix et al. (2015a), however the control group differed slightly in number, and this study did not include the medicated ADHD group for comparison. The sample consisted of 33 medication-naïve children with ADHD, compared to 27 TDC children, all between the ages of 7.9 and 12.9. The study compared ADHD and TDC volumes of gray matter, as well as investigated gender differences between the groups, hypothesizing that ADHD boys would display a decrease of GMV in the basal ganglia compared to controls, while ADHD girls would show decreases in the cerebellar vermis, as well as increases in the left lateral premotor cortex compared to TDC girls. A two-way ANOVA resulted in no significant differences in GMV between ADHD children and TDCs. However, when exploring gender differences, ADHD girls showed increased gray matter volume in the ACC compared to TDC girls, while ADHD boys showed decreased GMV compared to TDC boys in the same area.

Sutcubasi Kaya et al. (2016) studied 19 ADHD children and 18 TDCs, hypothesizing that although many previous studies have reported reductions of GMV in ADHD individuals, increases in some brain areas could also be associated with the disorder since it is not neurodegenerative. A two-sample t-test showed seven clusters in which ADHD children had greater GMV than controls; 1) the right precentral, superior frontal and middle frontal gyri, 2) the left supplementary motor area, 3) the left post- and precentral gyri, 4) the right middle occipital gyrus, 5) the left superior frontal gyrus, 6) the right supplementary motor area, and 7) the left cuneus. However, after cluster-level correction was applied, only the right precentral, superior frontal and middle frontal gyri remained significant.

Kumar et al. (2017) compared the GMV of 18 male 7.5 to 13-year-old ADHD children with an age-matched group of TDCs. Their findings suggested that ADHD children displayed lower total gray matter volume than the control group, but this difference was not significant. Regionally, however, VBM found GMV decreases in the ADHD group in four brain areas. Gray matter volume was lower in the left orbitofrontal cortex, the left middle/frontal dorsolateral prefrontal cortex, the left middle temporal cortex, and the left cerebellum.

Lastly, the sample Sáenz et al. (2020) studied consisted of children between the ages of 8 and 12, of whom 22 had ADHD and 17 were typically developing controls. Additionally, the sample included a group of 18 children with autism spectrum disorder (ASD). Sáenz et al. hypothesized that ADHD children would have lower overall gray matter volume than controls and that structural abnormalities in the cerebellum, as well as the left inferior frontal gyrus, would be disorder specific to the ADHD group. An analysis of variance found that the difference in total GMV was not statistically significant, but regionally, ADHD children had larger volumes of gray matter than TDCs in the left precuneus and right cerebellum. In the right thalamus and parahippocampal gyrus, however, the ADHD group exhibited smaller volumes than controls. Notably, these findings did not survive Bonferroni correction for multiple comparisons.

Table 1

Study Characteristics

Reference	Sample (n)	Gender	Mean Age (SD)	ROIs	Findings
Kumar et al. (2017)	ADHD: (n=18) TDC: (n=18)	All male	ADHD: 9.6 (1.8) TDC: 9.7 (1.9)	None	**Decrease** of GMV in: Total GMV (not significant) Left cerebellum Left middle frontal/DLPFC Left middle temporal cortex Left OFC
Makris et al. (2013)	ADHD: (n=24) TDC: (n=24)	ADHD: Male (n=15) Female (n=9) TDC: Matched	ADHD: 36.8 (12.1) TDC: 36.8 (12.9)	ACC Caudate nucleus Cerebellum DLPFC IPL/TOP OFC	Uncorrected: **Increase** of GMV in: DLPFC IPL/TOP OFC **Decrease** of GMV in: Dorsal ACC Caudate nucleus Cerebellum Corrected: **Decrease** of GMV in: Cerebellum
Montes et al. (2010)	ADHD: (n=20) TDC: (n=20)	ADHD: Male (n=10) Female (n=10) TDC: Matched	ADHD: 28.95 (4.01) TDC: 27.57 (2.6)	Right caudate nucleus	**Decrease** of GMV in: Part of right caudate nucleus
Sáenz et al. (2020)	ADHD: (n=22) TDC: (n=17)	ADHD: Male (n=16) Female (n=6) TDC: Male (n=12) Female (n=5)	ADHD: 10.17 (1.54) TDC: 10.51 (1.62)	None	Uncorrected: **Increase** of GMV in: Left precuneus Right cerebellum **Decrease** of GMV in: Right parahippocampal gyrus Right thalamus
Sutcubasi Kaya et al. (2016)	ADHD: (n=19) TDC: (n=18)	ADHD: Male (n=14) Female (n=5) TDC: Male (n=12) Female (n=6)	ADHD: 10.32 (1.95) TDC: 10.17 (2.04)	None	Uncorrected: **Increase** of GMV in: Right precentral gyrus Right superior frontal gyrus Right middle frontal gyrus Left supplementary motor area Left precentral gyrus Left postcentral gyrus Right middle occipital gyrus Left superior frontal gyrus Right supplementary motor area Left cuneus

					Corrected: **Increase** of GMV in: Right precentral gyrus Right superior frontal gyrus Right middle frontal gyrus
Villemonteix et al. (2015a)	ADHD: (n=33) TDC: (n=24)	ADHD: Male (n=18) Female (n=15) TDC: Male (n=12) Female (n=12)	ADHD: 10.3 (1.4) TDC: 10 (1.2)	Amygdala Caudate nucleus Nucleus accumbens	**Decrease** of GMV in: Right insula Right middle temporal lobe ROIs not significant
Villemonteix et al. (2015b)	ADHD: (n=33) TDC: (n=27)	ADHD: Male (n=18) Female (n=15) TDC: Male (n=13) Female (n=14)	ADHD: 10.3 (1.4) TDC: 9.82 (1.2)	ACC (Post-hoc)	No significant differences between ADHD and TDC GMV **Increase** of GMV in: ACC (girls) **Decrease** of GMV in: ACC (boys)

Note: All findings are in comparison to typically developing controls. ACC=anterior cingulate cortex; ADHD=attention deficit hyperactivity disorder; DLPFC=dorsolateral prefrontal cortex; GMV=gray matter volume; IPL/TOP=inferior parietal lobule/temporo-occipito-parietal region; OFC=orbitofrontal cortex; TDC=typically developing controls.

Discussion

The aim of this review was to investigate findings in MRI-based VBM studies, comparing gray matter volume between medication-naïve ADHD individuals and typically developing controls. The findings included increased GMV in a cluster containing the right precentral, superior frontal and middle frontal gyri (Sutcubasi Kaya et al., 2016), as well as in the anterior cingulate cortex, specifically for ADHD girls (Villemonteix et al., 2015b). Decreased GMV was exhibited in the cerebellum (Kumar et al., 2017; Makris et al., 2013), the left middle frontal/DLPFC, the left middle temporal cortex and the left OFC (Kumar et al., 2017). Reductions were also found in the right caudate nucleus (Montes et al., 2010), the insula and right middle temporal lobe (Villemonteix et al., 2015a), and lastly in the ACC of ADHD boys (Villemonteix et al., 2015b).

Some findings that did not remain significant after multiple corrections, but are worth noting include increases in GMV in the DLPFC, the lateral parieto-temporal cortex, and the OFC (Makris et al., 2013), the left precuneus and right cerebellum (Sáenz et al., 2020), the bilateral supplementary motor areas, the left pre- and postcentral gyri, the superior frontal gyrus, the left cuneus, and the right middle occipital gyrus (Sutcubasi Kaya et al., 2016). Decreases in GMV were also found, in the total brain volume (Kumar et al., 2017), the dorsal ACC, the caudate nucleus (Makris et al., 2013), the right parahippocampal gyrus, and the right thalamus (Sáenz et al., 2020).

Gray Matter Volume of the Cerebellum

The cerebellum is most commonly known for facilitating motor functions and balance but is also involved in several cognitive functions. It has an abundance of connections to cortical and subcortical structures including the prefrontal cortex, the posterior parietal cortex and the basal ganglia. Cerebellar abnormalities or damage have not only been connected to impaired coordination of movements but also to impaired executive functioning and emotional regulation (Cundari et al., 2023). A review by Cundari et al. (2023) investigated the role of the cerebellum in three disorders, including ADHD. They reported both structural and functional cerebellar abnormalities in ADHD individuals, linking them to impaired performance in cognitive tasks involving executive functions like inhibition control and attention. In accordance with these findings, Kumar et al. (2017) and Makris et al. (2013) both found significantly decreased GMV in the cerebellum of ADHD children and adults respectively. In addition to measuring GMV, Kumar et al. (2017) also measured the severity of ADHD behavioral symptoms, using the Attention deficit hyperactivity disorder rating scale (ADHD RS) parent version (DuPaul et al., 1998). They found that GMV of the left cerebellum was negatively correlated with scores in both parent-rated subscales; inattentiveness and impulsivity/hyperactivity, suggesting that reduced cerebellar GMV may be connected to ADHD.

Gray Matter Volume of the Anterior Cingulate Cortex

The anterior cingulate cortex has connections to both the prefrontal cortex and the limbic system, receiving both cognitive and emotional information. This indicates the involvement of the ACC in emotional regulation (Stevens et al., 2011). Lesion studies have also listed inattention as a symptom of ACC damage (Bush et al., 2000). Reduced GMV of the ACC has been reported by Bonath et al. (2016), who investigated adolescents with ADHD. They also, through clinical measures, found a positive correlation between GMV of the ACC and performance in a selective attention task. This correlation was prevalent in the ADHD group, but not among the typically developing controls. Makris et al. (2013) and Villemonteix et al. (2015b) similarly reported GMV differences in the ACC. Makris et al. (2013) found decreased GMV in the dorsal part of the ACC in ADHD adults at an uncorrected threshold of significance, while Villemonteix et al. (2015b) found significant GMV differences within the ventral ACC of ADHD children. This difference was also gender specific, with ADHD girls displaying increased GMV compared to TDC girls, the opposite being the case in boys. Villemonteix et al. (2015b) suggest that these gender differences may be connected to ADHD boys more commonly displaying externalizing symptoms such as aggression, while ADHD girls are more prone to internalizing symptoms. The differences in findings across the two studies may be due to the sample Makris et al. (2013) utilized containing a higher percentage of males, possibly accounting for more of a tendency towards GMV decrease.

Gray Matter Volume of the Caudate Nucleus

The caudate nucleus is implicated in functions such as motivation, reward, learning and planning movement execution (Driscoll et al., 2023). It forms together with the putamen the dorsal striatum, which is part of the basal ganglia. Involved in circuits crucial to executive functions, animal studies of striatal lesions have reported the damage to be associated with ADHD-like symptoms, such as impaired working memory and response inhibition, as well as increased hyperactivity (Seidman et al., 2011). The dorsal striatum is also part of the nigrostriatal dopaminergic pathway, most commonly associated with Parkinson's disease, where there is atrophy of dopaminergic neurons in both the caudate and the putamen

(Driscoll et al., 2023; Marsden, 2006). Due to its dopaminergic properties, the caudate is relevant in the stimulant treatment of ADHD, which acts by blocking dopamine transporters in the basal ganglia, resulting in increased levels of striatal dopamine (Nakao et al., 2011). When controlling for medication in their meta-analysis, Nakao et al. (2011) found that the percentage of participants undergoing stimulant treatment predicted more normalized GMV in the striatum (specifically the right caudate). When controlling separately for age, they found that increasing age also was associated with normalized striatal GMV (in the right putamen). This is interesting since Montes et al. (2010) and Makris et al. (2013) were the only two studies conducted on adult ADHD individuals, and also the only ones who found decreased GMV in the caudate nucleus (although the latter did not remain significant after correction).

Montes et al. (2010) measured gray matter concentration (GMC) in addition to GMV, locating a portion of the right caudate in which GMC was lower in ADHD adults compared to typically developing controls. This portion also had statistically lower GMV. The study also involved clinical measures, and when investigating correlations between DSM-IV-TR criteria and GMV of the right caudate, impulsivity, hyperactivity and inattention were associated with lower GMV across the whole sample. Finding smaller caudate volumes than in TDCs in a medication-naïve sample is consistent with the findings of Nakao et al. (2011) regarding the effects of stimulant treatment, although granted, the samples used in Makris et al. (2013) and Montes et al. (2010) were not compared to a medicated equivalent. Finding smaller caudates in adults, but not in children (albeit within the constraints of this review), however, is contradictory to the suggested effect of volume normalization with increasing age. Seidman et al. (2011) also observed smaller caudate GMV in their regional VBM-study on an adult sample with varying medication history, 30% being medication-naïve. Depending on to what extent pharmacological treatment affects GMV, decreased caudate volume in adults may be a possible neural correlate of ADHD.

Limitations and Future Prospects

This review aimed to remove the factor of varying history of pharmacological treatment in ADHD samples, in an attempt to combat the many different, sometimes contradictory findings about the structural correlates of ADHD. However, the inclusion of only medication-naïve samples did not particularly increase the homogeneity of the findings. Although some overlap in the way of decreased gray matter volume occurred, the majority of the findings did not coincide with each other. For example, the significant increases of GMV found by Sutcubasi Kaya et al. (2016) were not supported by any of the other studies. This may be due to it being the only study attempting to find specifically increased gray matter volume. There were also contradictory findings. For example, Kumar et al. (2017) reported decreased volumes of the OFC and DLPFC, while Makris et al. (2013) reported increases in these areas.

Overall the review is limited in the included studies' fairly small sample sizes, as well as the small number of studies in general. There is also the aspect of age, as previously discussed. Only two out of the seven included studies were conducted on adults. No exclusion criterion was formatted age-wise, mainly to be able to include as many medication-naïve samples as possible. Nakao et al. (2011) and Yu et al. (2023) included both children and adults, but due to their larger inclusion of studies of both age groups were perhaps able to generalize on a more extensive level than the present review can. Our findings do, however, highlight the importance of future research adjusting their experimental design to account for the difficulty in distinguishing disorder-specific GMV abnormalities from developmental changes or normalization due to treatment. An avenue for future research may lie in a longitudinal follow-up paradigm, comparing medication-naïve versus medicated ADHD individuals through MRI at both time points of childhood/adolescence and adulthood.

Gender distribution should also be noted as something possibly affecting the findings. All but one study included both males and females, but as Villemonteix et al. (2015b) suggest, there may be gender differences in how ADHD structurally presents itself in the brain.

Another limitation is the fact that this review did not focus on distinguishing between or comparing ADHD subtypes (inattentive, impulsive/hyperactive and combined types), nor did any of the included studies. There could be variations in GMV differences across these subtypes, something future studies may wish to investigate.

Lastly, ADHD as a disorder presents very heterogeneously. With a range of possible symptoms, neuroimaging findings become more difficult to generalize. Sudre et al. (2018) also bring up the point that ADHD is considered remitted at the point where symptoms no longer meet enough of the diagnostic criteria, meaning one can still experience up to four symptoms causing considerable impairment in everyday life. Focusing research more on ADHD symptoms or traits, such as investigating specifically the neural correlates of inattention, impulsivity or hyperactivity may result in more robust findings than a diagnosis versus healthy control comparison. This may also be more beneficial to develop treatment that focuses on specific impairments.

Social and Ethical Aspects

Elucidating what brain abnormalities are actually associated with ADHD as a disorder, and are not caused by external factors, is crucial to better help ADHD individuals suffering from their cognitive impairments. However, one must also take social aspects into account. A recent commentary by Dekkers (2024) argues that a paradigm shift in how ADHD is viewed societally is needed, promoting the theory of the disorder as a social construct. He emphasizes that social and cultural factors like poverty, trauma, and screen time should receive more attention to avoid children being put in a position of stigma, pessimism for their future prospects and reliance on stimulant medication. Roganin and Nencini (2014) interviewed educators on the upsides and downsides of labeling children with an ADHD diagnosis. Subjects stated that the diagnosis helped in understanding the child's behavior, both from an educator and peer-perspective. This made it more unlikely for the child to be labeled as a "rowdy kid" causing disturbances. Educators also stated that diagnosis helped bring their attention to what the individual needs of the child were. Simultaneously they

recognized that an ADHD diagnosis somewhat resembles a criminal record, in the sense that it can limit an individual's identity and what they are expected to be able to accomplish (Roganin & Nencini, 2014). The social perspective of ADHD may be more compatible with trait- or symptom-focused research rather than comparison between ADHD individuals and typically developing controls, and trying to identify the underlying mechanisms of inattention, impulsivity, hyperactivity and impairments of various cognitive functions, to get to the root of what causes decreased well-being in individuals with the diagnosis.

Conclusion

The findings of the present review agree with previous studies that ADHD individuals exhibit differences in gray matter volume compared to typically developing controls, including decreased volume of the cerebellum, potential gender-wise GMV-differences in the anterior cingulate cortex, and decreased volume of the caudate nucleus in adults, suggesting a correlate of ADHD that perhaps does not normalize with developmental maturation. Taking into account the limitations of this review, along with the fact that the heterogeneous nature of the disorder complicates the interpretation of the results, the body of research conducted on medication-naïve samples, as well as how development affects GMV, needs to expand to be able to draw more robust empirical conclusions in the future. Focusing on symptom or trait-wise neural correlates rather than diagnostic ones may also combat heterogeneity, as well as incorporate social theory of ADHD better.

Final word count: 5501 words

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