Neuroanatomical Differences Between Girls and Boys with Attention-Deficit Hyperactivity Disorder: A Critical Review and Implications for Treatment

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is a childhood neurodevelopmental disorder characterized by developmentally inappropriate levels of inattention, hyperactivity, and impulsivity (Diagnostic and Statistical Manual of Mental Disorders; 5th ed., American Psychiatric Association, 2013). About 5% of school age children are diagnosed with this disorder and about 65% will have symptoms that persist beyond adolescence (Friedman & Rapport, 2015). Although girls with ADHD exhibit different symptoms relative to boys with ADHD, there is a lack of research on sex-differences in ADHD-related neuroanatomical structures. There is evidence, however, that girls with ADHD have a 10% decrease in total cerebral gray matter volume compared to boys with ADHD, although they peak 3.5 years earlier than boys (Mahone & Wodka, 2008). Given that teachers rate boys as having more severe ADHD symptomatology compared to girls (Gaub & Carlson, 1997), it is necessary to inform educators on peak maturational age differences to ensure successful referrals. This review focuses on neuroanatomical differences between boys and girls with ADHD and summarizes results from 50 articles between 1999-2017. Deficits in neuroanatomical structures and levels of functioning are identified. Implications for future research and treatment options will be discussed.

Introduction

ADHD

- About 5% of school age children diagnosed with ADHD (Friedman & Rapport, 2015)
- 65% have symptoms persisting beyond adolescence (Friedman & Rapport, 2015)
- Children with ADHD have neuroanatomical differences from typically developing children (Shaw et al., 2007, Witt & Stevens, 2015, Greven et al., 2015, Castellanos & Acosta, 2004, Kasparek et al., 2015, Valera et al., 2007, Kumar et al., 2017)

NEGATIVE IMPACT

- ADHD can greatly affect an individual's
  - Academic achievement (McGee & Feehan, 1991, Biederman et al., 1999)
  - Mental health (Biederman et al., 1999)
  - Social skills (McGee & Feehan, 1991, Biederman et al., 1999)
- Children with ADHD have deficits in alertness, selective attention, divided attention, and sustained attention (Pitzianti et al., 2016)

BOYS WITH ADHD

- 2.3 times more likely to be diagnosed with ADHD (Bauermeister et al., 2007)
- More pronounced symptoms (Mahone & Wodka, 2008)
- More cognitive delay than girls with ADHD (Mahone & Wodka, 2008)

GIRLS WITH ADHD

- Poorer outcomes (Mahone & Wodka, 2008) such as higher instances of depressive and anxiety disorders (Gaub & Carlson, 1997, and Gershon, 2002)

WHY WE NEED TO LOOK AT GIRLS WITH ADHD DIFFERENTLY

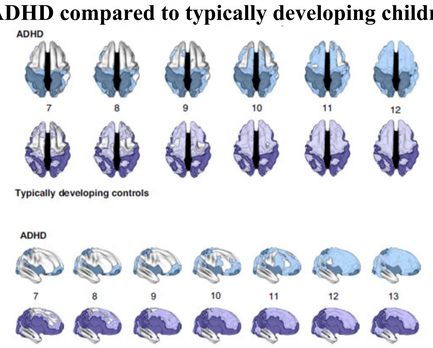
- Significant neuroanatomical differences between boys and girls with ADHD (Mahone & Wodka, 2008, Castellanos et al., 2002, Giedd et al., 1999, Villemonteix et al., 2015, van Ewijk et al., 2015)
- Research on neuroanatomical differences between boys and girls with ADHD may play vital role in developing more specialized methods of diagnosis and treatment for girls with ADHD (Gaub & Carlson, 1997)

Methods

We used Google Scholar and PsychINFO to find relevant articles. We used the search terms 'ADHD', 'neuroanatomical', and 'girls'. To refine the search, we specified the date range as 1997-2017.

We found 59 articles directly applicable to our topic. Fourteen articles were later excluded because upon further review, they did not contain information pertinent to our focus. After exclusions, 45 articles were included in this review. The articles excluded lacked information on girls with ADHD, did not evaluate parent and teacher ratings, or did not include statements about psychostimulant medication.

Figure 1: Age of attaining peak cortical thickness in children with ADHD compared to typically developing children



(Shaw et al., 2007)

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Neuroanatomical Differences in Girls with ADHD

- Difficult for parents and teachers to recognize girls with ADHD because their maturation is similar to that of a typically developing boys of the same age
- While girls with ADHD have fewer symptoms than boys with ADHD as children, during puberty, the increase of dopamine receptors caused by the increase in estrogen may lead to an increase in symptoms in adolescence (Mahone & Wodka, 2008)
- See Table 1 for distinctions in neuroanatomical differences in ADHD

Table 1: Neuroanatomical Differences in Girls with ADHD

		Function of Brain Region	Girls with ADHD	Boys with ADHD
Patterns of Cerebral Organization		Right hemisphere specialized in verbal and linguistic processes Left hemisphere specialized in nonverbal processes (Bryden et al., 1983)	More right-lateralized asymmetry pattern than typically developing (Mahone & Wodka, 2008)	Less right-lateralized asymmetry pattern than typically developing (Mahone & Wodka, 2008)
Theta Activity		Associated with episodic and working memory tasks (Jensen & Tesche, 2002)	Localized frontal enhancement (Mahone & Wodka, 2008)	Widespread increase (Mahone & Wodka, 2008)
Cortical Surface Area	**Prefrontal Cortex**	Regulates thoughts, behavior, and emotions (Arnsten, 2009)	Smaller surface area than typically developing in more regions (Dirlikov et al., 2015)	Smaller surface area than typically developing in fewer regions (Dirlikov et al., 2015)
	Premotor Cortex	Regulates motor output; Has attentional and receptive functions (Schubotz & Cramon, 2003)	Same surface area as typically developing (Dirlikov et al., 2015)	Smaller surface area than typically developing (Dirlikov et al., 2015)
Cortical Volume		Significant positive correlation with intelligence performance (Walhovd et al., 2005)	Same as typically developing (Mahone & Wodka, 2008)	Smaller than typically developing (Mahone & Wodka, 2008)
Grey Matter Volume	**Left Lateral Premotor Cortex**	Implicated in self control (Figner et al., 2010)	Smaller than typically developing (Mahone et al., 2011)	Same as typically developing (Mahone et al., 2011)
	Ventral Anterior Cingulate Cortex	Emotional self-control, focused problem-solving, error recognition, adaptive response (Allman et al., 2001)	Larger than typically developing (Villemonteix et al., 2015)	Smaller than typically developing (Villemonteix et al., 2015)
White Matter Volume in Left Lateral Premotor Cortex		Implicated in self control (Figner et al., 2010)	Same as typically developing (Mahone et al., 2011)	Smaller than typically developing (Mahone et al., 2011)

Neuroanatomical Differences in Children with ADHD

MRI FINDINGS

- Most common method of examining the pediatric brain (Krain et al., 2006)
- Derives information on exact brain connectivity (Griffiths et al., 2016)
- Neuroimaging methods are increasingly used to study ADHD (Ercan et al., 2016)

MATURATIONAL DELAYS

- Those with ADHD showed significant delays in achieving peak cortical thickness (See Figure 1) (Shaw et al., 2007)
  - Most prominent delay is in the lateral prefrontal cortex (Shaw et al., 2007)
    - Prefrontal cortex contains a variety of cognitive functions such as executive attentional control, working memory, and inhibition (Shaw et al., 2007)
    - May be attributed to genetic factors (Shaw et al., 2014)

NEUROSTRUCTURAL REDUCTION

- Multiple neurostructural areas in children with ADHD
  - Have smaller surface area
  - Do not progress with age (Shaw et al., 2014)
- Cortical thinning is prominent and shows abnormalities in multiple cortical areas (Kumar et al., 2017)
- Measures of white matter integrity are linearly linked to ADHD symptom severity (Witt et al., 2015) (See Figure 2)
- Children with ADHD have a 3% decrease in total gray matter volume (Greven et al., 2015)
  - Gray matter contains neuronal cell bodies, dendrites, and axon terminals, and is where synapses are located whereas white matter contains axons that connect parts of gray matter together (Indiana University, http://www.indiana.edu/~p1013447/dictionary/greywhit.htm)

REDUCTION IN TOTAL BRAIN VOLUME

- Overall reductions of total brain volume in ADHD patients compared to age-matched controls (Castellanos & Acosta, 2004)
- Total brain volume continuously decreases in those with ADHD from childhood to adolescence (Kasparek et al., 2015)

ADHD in Girls vs. Boys

- Girls have ~10% less total cerebral gray matter volume compared to boys (Mahone & Wodka, 2008)
- Girls peak in total cerebral gray matter 3.5 years earlier than boys (Mahone & Wodka, 2008)
- Gender differences mostly found in the frontal brain region, where males have higher activation (van Ewijk et al., 2015).
- See Table 2 to differentiate gender differences between boys and girls with ADHD

Table 2: Gender Differences in Symptoms, Diagnosis, and Outcomes

	Girls with ADHD	Boys with ADHD
Symptoms	Fewer hyperactive symptoms (Gaub & Carlson, 1997, and Gershon, 2002)	More hyperactive symptoms (Gaub & Carlson, 1997, and Gershon, 2002)
	Less motor impairment (Dirlikov et al., 2015)	Greater motor impairment (Dirlikov et al., 2015)
	Less effortful response inhibition impairment (Dirlikov et al., 2015)	Greater effortful response inhibition impairment (Dirlikov et al., 2015)
	More inattentive symptoms (Gaub & Carlson, 1997, and Gershon, 2002)	Fewer inattentive symptoms (Gaub & Carlson, 1997, and Gershon, 2002)
	Greater higher-order cognitive deficits, (Dirlikov et al., 2015)	Fewer higher-order cognitive deficits (Dirlikov et al., 2015)
Diagnosis	Less commonly diagnosed (Gaub & Carlson, 1997)	More commonly diagnosed (Gaub & Carlson, 1997)
Outcomes	Greater peer rejection (Gaub & Carlson, 1997)	Less peer rejection (Gaub & Carlson, 1997)
	Higher risk for future psychological problems (Rucklidge & Tannock, 2001)	Lower risk for future psychological problems (Rucklidge & Tannock, 2001)
	Higher instances of depressive and anxiety disorders (Gaub & Carlson, 1997, and Gershon, 2002)	Lower instances of depressive and anxiety disorders (Gaub & Carlson, 1997, and Gershon, 2002)

Parent and Teacher Evaluations

- Parent and Teacher ratings commonly used for ADHD diagnosis
- Ratings often used as a measure of symptomatology for research on ADHD
- Parents and teachers rate boys with ADHD as more deviant than girls with ADHD on levels of inattention and hyperactivity (Gaub & Carlson, 1997, and Gershon, 2002)
- Teachers rate boys as having higher ADHD symptomatology compared to girls (Gaub & Carlson, 1997), and as displaying fewer externalizing symptoms (Gershon, 2002)
- Necessary to inform educators on peak maturational age differences to ensure successful referrals
- Average effect size differences between boys and girls were significantly larger for teacher evaluations, when compared to parent evaluations (Gaub & Carlson, 1997)
- Elementary school teachers, and parents, should be educated on recognizing symptoms and the different manifestation between the genders (Gershon, 2002)

Implications for Treatment

LACK OF RESEARCH ON GIRLS

- Girls tend to 'age out' of symptoms earlier than boys (Mahone & Wodka, 2008)
- May contribute to the general lack of conclusions (Mahone & Wodka, 2008)
- Lack of research on girls with ADHD contributes to the absence of a clear pattern of brain dysfunction and behavioral deficits

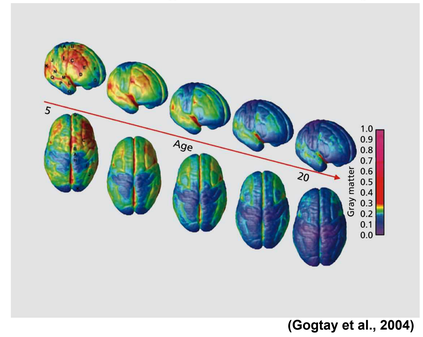
COMMUNITY VS. CLINICAL SAMPLES

- It is necessary that researchers focus on community based populations as well as clinic referrals
- Children referred from a clinical sample tend to have more pronounced symptomatology (Gaub & Carlson, 1997, and Gershon, 2002)
- When taking into account community samples only, girls are rated less impaired than boys (Gershon, 2002)

GENDER DIFFERENCES

- Gender differences have been reported regarding the different ADHD subtypes (ADHD-C vs. ADHD-I) (Gershon, 2002)
- Future research needs to consider the examination of gender differences in the DSM (Gershon, 2002)
- Longitudinal gender studies would be beneficial to psychology research to further understand structural ADHD differences
- Gender differences have been reported regarding externalizing and internalizing behaviors (Gershon, 2002)
- Different comorbid conditions would be expected between the genders; assessment of these comorbid disorders is necessary (Gershon, 2002)

Figure 2: Gray matter maturation between ages five and twenty



(Gogtay et al., 2004)

Implications for Research

PARENT AND TEACHER RATINGS

- The classroom tends to be the first place where disruptive symptoms are identified (Gershon, 2002)
- Further research is needed to evaluate the effectiveness of parent and teacher rating scales to ensure proper diagnosis and treatment

RESEARCH ON GIRLS WITH ADHD

- Lack of information has serious implications because there are various long term effects of ADHD, such as social, academic, and emotional difficulties (McGee & Feehan, 1991)
- Necessary to study boys and girls at their average onset of peak ADHD symptomatology to ensure proper diagnoses and treatment protocol

Summary and Conclusion

The lack of research on girls with ADHD is pronounced. It is necessary to continue to research girls with ADHD because the symptoms, course, severity, and social effects are different than in boys. Specifically, anatomical, functional, cognitive, and behavioral research is needed to elaborate on neurological differences between boys and girls (Dirlikov et al., 2015). Neuroanatomical research has found results critical to the understanding of ADHD. These include maturational differences between boys and girls, as well as neuroanatomical differences in girls with ADHD (Mahone & Wodka, 2008). Even though boys with ADHD have more pronounced symptoms and more cognitive delay (Mahone & Wodka, 2008), girls with ADHD have poorer outcomes (Mahone & Wodka, 2008), so it is imperative they receive proper diagnosis. It is important to educate teachers, caregivers, and parents about these findings to improve their ability to identify symptoms of ADHD in girls to ensure a proper diagnosis and treatment course.

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