

Electronic Thesis and Dissertation Repository

4-8-2021 3:00 PM

Adversity, Neurodevelopment, and Cognition in Attention Deficit Hyperactivity Disorder

Alissa Papadopoulos, *The University of Western Ontario*

Supervisor: Duerden, Emma G., *The University of Western Ontario*

A thesis submitted in partial fulfillment of the requirements for the Master of Arts degree in Education

© Alissa Papadopoulos 2021

Follow this and additional works at: <https://ir.lib.uwo.ca/etd>



Part of the [Development Studies Commons](#)

Recommended Citation

Papadopoulos, Alissa, "Adversity, Neurodevelopment, and Cognition in Attention Deficit Hyperactivity Disorder" (2021). *Electronic Thesis and Dissertation Repository*. 7705.

<https://ir.lib.uwo.ca/etd/7705>

This Dissertation/Thesis is brought to you for free and open access by Scholarship@Western. It has been accepted for inclusion in Electronic Thesis and Dissertation Repository by an authorized administrator of Scholarship@Western. For more information, please contact wlsadmin@uwo.ca.

Abstract

Problem behaviours associated with Attention Deficit Hyperactivity Disorder (ADHD) symptomatology put children at increased risk of experiencing peer victimization, which has been associated with altered brain development and cognitive ability. A large sample of typically developing (TD), ADHD combined type (ADHD-C), and ADHD inattentive type (ADHD-I) children underwent behavioural assessment, magnetic resonance imaging (MRI) and cognitive testing. We examined how problem behaviours and peer victimization differed among the groups, how problem behaviours and peer victimization related to hippocampal volume, and how hippocampal volume related to working memory (WM). The ADHD-C group displayed the highest levels of peer victimization and problem behaviours. We found that left Cornu Ammonis 3 (CA3) volume was a positive predictor of peer victimization and of WM ability, while left Cornu Ammonis 4 (CA4) negatively predicted WM. Interventions targeting peer victimization in schools may help reduce adverse brain and cognitive outcomes, particularly in children with ADHD-C.

Keywords

Attention Deficit Hyperactivity Disorder, Executive Functioning, Externalizing Behaviour, Hippocampus, Hyperactivity-Impulsivity, Inattention, Mental Health, Peer Victimization, Working Memory.

Summary for Lay Audience

Attention Deficit Hyperactivity disorder (ADHD) consists of three different subtypes including ADHD Inattentive type (ADHD-I) characterized by elevated symptoms of inattention, ADHD Hyperactive-Impulsive type (ADHD-H), characterized by elevated symptoms of hyperactivity-impulsivity, and ADHD Combined type (ADHD-C), characterized by elevated symptoms in both domains. Many children and adolescents with ADHD have social difficulties, however children with more severe hyperactive-impulsive symptoms display more problem behaviours, like talking out of turn and not following rules, that increase their risk of experiencing bullying by their peers. Peer victimization can cause severe stress, and even alter the development of a brain region, known as the hippocampus, which is involved in learning and memory. In turn children with ADHD may be at risk for social problems, stress, and alterations in brain development and working memory (WM). This thesis addressed three main aims. First, we examined how levels of problem behaviours and peer victimization differ between typically developing (TD) children and those with two different ADHD subtypes, including ADHD-I and ADHD-C. Our second aim was to examine whether hippocampal size was related to levels of problem behaviours and peer victimization. Our third aim was to examine if hippocampal volume could predict WM abilities. We found that the ADHD-C group displayed the most severe levels of problem behaviour and experienced the most peer victimization. We also found that regional alterations in the development of the hippocampus was associated with peer victimization and WM. This suggests that school-based interventions aimed at reducing peer victimization in schools may be key to promoting brain and cognitive health.

Co-Authorship Statement

Chapter 2 was adapted from the manuscript title “Peer victimization and the association with hippocampal development and working memory in children with and without ADHD” that is under review at *Neuroimage: Clinical*. The co-authors of the paper are Diane Seguin, Susana Correa, and Emma G. Duerden. Diane Seguin and Emma G. Duerden were involved in study design and conception. Susana Correa was involved in pre-processing of Magnetic Resonance Imaging data. I, Alissa Papadopoulos, was involved in study design and conception, as well as data analysis, interpretation and the writing of the complete manuscript.

Acknowledgements

I want to thank my thesis advisor, Dr. Emma G. Duerden, for her constant support, guidance, and encouragement. I feel grateful to have had the opportunity to join her lab and to work on this project, as well as other exciting projects throughout the past two years. I would also like to thank my lab members Diane Seguin and Emily Nichols, for their support and helpful feedback. I would also like to thank my lab member Susana Correa for collecting and processing the project's MRI data.

I want to thank my classmates and friends, Bernadette, Jasmyn, Kelsey, and Maria for their support and friendship throughout this journey. I want to thank my lifelong friend Sarah for her unwavering support and for always encouraging and believing in me.

I would also like to thank my partner Artem for fully supporting my decision to pursue this master's degree and in helping keep me calm throughout this process. I would also like to thank my parents, Dino and Anna, and my brother, James, for always being my number one fans and for giving me the confidence to pursue my goals. I cannot forget to thank my dog Jasper, who sat right beside me in the completion of this project and degree, every step of the way.

Lastly, I would like to acknowledge the Child Mind Institute for collecting the data used for this project, without which this would not be possible.

Table of Contents

Abstract	ii
Summary for Lay Audience	iii
Co-Authorship Statement.....	iv
Acknowledgements	v
List of Tables	ix
List of Figures	x
List of Appendices	xi
List of Abbreviations	xii
1 Introduction.....	1
1.1 ADHD subtypes	2
1.2 Problem behaviour and ADHD subtypes.....	3
1.3 Peer victimization and ADHD subtypes	4
1.4 ADHD, peer victimization and hippocampal morphology	5
1.5 Hippocampal morphology and working memory	7
1.6 The current study	8
1.7 References.....	10
2 Experiment: Peer victimization and the association with hippocampal development and working memory in children with and without ADHD	16
2.1 Introduction.....	16

2.2 Methods.....	19
2.2.1 Participants.....	19
2.2.2 Procedures.....	22
2.2.3 Demographic Measures	22
2.2.4 Psychological Measures.....	23
2.2.5 Magnetic Resonance Imaging.....	23
2.2.6 Hippocampal Segmentation.....	24
2.2.7 Statistical Analysis.....	24
2.3 Results.....	25
2.3.1 Participant Demographics	25
2.3.2 Problem Behaviours, Peer Victimization and Diagnostic Group	25
2.3.3 Problem Behaviours, Peer Victimization and Hippocampal Subfield Volumes	28
2.3.4 Hippocampal Subfield Volumes and Working Memory Ability	28
2.3.5 Post-Hoc Cluster Analysis	29
2.4 Discussion.....	33
2.4.1 Problem Behaviours, Peer Victimization and Diagnostic Group	34
2.4.2 Hippocampal Subfield Volume, Problem Behaviours and Peer Victimization	35
2.4.3 Hippocampal Subfield Volume and Working Memory.....	37
2.4.4 ADHD Subtypes, Hippocampal volumes, Working memory and Peer Victimization	38
2.4.5 Limitations	39
2.5 Key Points.....	40
2.6 References.....	41

3 Discussion	47
3.1 Implications.....	47
3.2 Future directions	49
3.3 Conclusions.....	52
3.4 References.....	54
Appendices.....	56
Appendix A: Child Mind Institute Biobank Data Transfer Agreement.....	56
Appendix B: Child Behaviour Checklist (CBCL)	57
Appendix C: Strengths and Weaknesses Assessment of ADHD and Normal Behaviour (SWAN)	61
Appendix D: Wechsler Intelligence Scale for Children-V (WISC-V) Working Memory Index	62
Curriculum Vitae	63

List of Tables

Table 1. Characteristics of TD, ADHD-C and ADHD-I participants.....	20
Table 2. Three-Cluster Model Participant Demographics.	30

List of Figures

Figure 1. Problem Behaviours and Peer Victimization in Diagnostic Groups.	27
Figure 2. K-means Clustering based on Peer Victimization, Left CA3, WMI, Hyperactivity- Impulsivity and Inattention.	32

List of Appendices

Appendix A: Child Mind Institute Biobank Data Transfer Agreement.....	56
Appendix B: Child Behaviour Checklist (CBCL)	57
Appendix C: Strengths and Weaknesses Assessment of ADHD and Normal Behaviour (SWAN)	61
Appendix D: Wechsler Intelligence Scale for Children-V (WISC-V) Working Memory Index .	62

List of Abbreviations

Abbreviation	Meaning
ADHD	Attention Deficit Hyperactivity Disorder
ADHD-I	Attention Deficit Hyperactivity Disorder Inattentive Type
ADHD-H	Attention Deficit Hyperactivity Disorder Hyperactive-Impulsive Type
ADHD-C	Attention Deficit Hyperactivity Disorder Combined Type
ANOVA	Analysis of Variance
ASD	Autism Spectrum Disorder
B	Standardized Coefficient
BSMSS	Barratt Simplified Measure of Social Status
CA1	Cornu Ammonis 1
CA3	Cornu Ammonis 3
CA4	Cornu Ammonis 4
CBCL	Child Behaviour Checklist
CBIC	Citigroup Biomedical Imaging Center
DG	Dentate Gyrus
FSIQ	Full-scale Intelligence Quotient
GCMLDG	granule cell layers of the dentate gyrus
GCs	Glucocorticoids
HATA	hippocampus-amygdala-transition-area
IQ	Intelligence Quotient
IQR	Interquartile Range
K-SADS-COMP	Kiddie Schedule for Affective Disorders and Schizophrenia
MRI	Magnetic Resonance Imaging
n	Number of Participants
ODD	Oppositional Defiant Disorder
p	Probability
PTSD	Post-Traumatic Stress Disorder
RU	Rutgers University
SD	Standard Deviation
SES	Socioeconomic Status
SI	Staten Island Diagnostic Research Center
SWAN	Strengths and Weaknesses Assessment of ADHD and Normal Behaviour
TCV	Total cerebral volume
TD	Typically Developing
WISC-V	Wechsler Intelligence Scale for Children, Fifth Edition
WM	Working Memory
WMI	Working Memory Index
95%CI	95% Confidence Interval

Chapter 1

1 Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is an early onset neurodevelopmental disorder that differentially affects males and females at a ratio of 2:1 and is approximated to have a worldwide prevalence of 5% (American Psychiatric Association [APA], 2013; Biederman & Faraone, 2005; Polanczyk et al., 2007). The aetiology of ADHD is under active investigation. Although, the disorder has been shown to be highly heritable. Evidence also suggests that environmental factors, such as the stress associated with adversity such as maltreatment, abuse, and neglect, are implicated in both the disorder's aetiology and symptomatology (Thapar et al., 2012; Biederman & Faraone, 2005). Single adverse episodes or ongoing exposure to adversity such as maltreatment, neglect, and abuse in childhood and adolescence can cause significantly heightened levels of stress that represent a deviation from the typical environment required for healthy development (McLaughlin, 2016). Many studies demonstrate the relationship between adversity and ADHD by providing evidence that children and youth with ADHD experience statistically higher levels of adversity than those who are typically developing (TD) (Björkenstam et al., 2017; Brown et al., 2017; Foley, 2011).

Peer victimization is a common type of adversity but has been understudied in children and youth with ADHD. Recent research has suggested that children and youth with ADHD are the most at-risk pediatric population for peer victimization (Blake et al., 2016; Frankel & Feinberg, 2002; Humphrey et al., 2007; Winters et al., 2020). In general, decreased brain volumes have frequently been seen in ADHD populations compared to TD populations (Shaw et al., 2007). Evidence also suggests that higher levels of peer victimization are associated with smaller brain volumes (Lee et al., 2018; Teicher et al., 2018). However, there remains

uncertainty about how peer victimization is associated with brain volumes in children with and without ADHD. Although understudied in the peer victimization and broader adversity literature, a critical brain region is the hippocampus, because of its sensitivity to stress (Dahmen et al., 2018; Sapolsky, 2000). The hippocampus is also a brain region of interest because it is involved in many executive functions, including working memory (WM) (McDaniel, 2005; Van Petten, 2004). There remains uncertainty as to how the volume of the hippocampus might impact cognitive functioning, especially in pediatric populations (McDaniel, 2005; Van Petten, 2004). Some studies suggest that decreased hippocampal volume may result in cognitive deficits, particularly in WM, otherwise some studies have found negative relationships between hippocampal volume and WM; a consensus has not been reached (Beauchamp et al., 2008; Van Petten, 2004).

1.1 ADHD subtypes

In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), ADHD symptoms are divided into two categories, including inattention and hyperactivity-impulsivity (APA, 2013). Nine symptoms are included in the DSM-5 for inattention, briefly summarized these include: making careless errors, failing to finish tasks, losing things often, avoidance and dislike of activities that require long periods of stillness, forgetfulness, becoming easily distracted, difficulties in sustaining attention, and trouble with organization. Additionally, nine symptoms are included for hyperactivity-impulsivity. They include trouble sitting still, leaving situations where being still is required, restlessness and inserting oneself into situations inappropriately, lacking control, intrusiveness and interrupting, excessive talking, impatience, inability to quietly engage in activities, and being a difficult individual to keep up with (APA, 2013). ADHD is diagnosed when at least six symptoms are present in either category or six or

more symptoms are present in both categories, and when the symptoms have been present before 12 years of age (APA, 2013). In addition, the symptoms have to significantly impair functioning in at least two different settings in the individual's life, for example at home and in school, school and at work, social relationships and school, etc. (APA, 2013).

In the DSM-5, ADHD diagnoses are further divided into clinical subtypes based on symptomatology. Individuals presenting with six or more symptoms in both the inattention and hyperactivity-impulsivity domains are categorized as ADHD Combined type (ADHD-C) (APA, 2013). Those with six or more symptoms in the inattention domain, but fewer than six symptoms in the hyperactivity-impulsivity domain are categorized as ADHD Inattentive type (ADHD-I) and those with six or more symptoms in the hyperactivity-impulsivity domain, and fewer than six symptoms in the inattention domain are categorized as ADHD Hyperactive-Impulsive type (ADHD-H) (APA, 2013).

1.2 Problem behaviour and ADHD subtypes

Notable differences in behavioural profiles among the ADHD subtypes have been reported (Deotto et al., 2021; Gaub & Carlson, 1997). Children with subtypes of ADHD, associated with more severely elevated symptoms of hyperactivity-impulsivity, including ADHD-C and ADHD-H, have been found to exhibit higher levels of externalizing behaviours than children with the ADHD-I subtype (Deotto et al., 2021; Gaub & Carlson, 1997). In addition, children with the ADHD-H subtype, and particularly those with the ADHD-C subtype, have been found to have more conduct problems and exhibit more difficulties in social settings than children with ADHD-I (Gaub & Carlson, 1997; Rostami et al., 2020). In a study by Gaub & Carlson (1997), the ADHD-C subtype was seen to be the most anxious and depressed however this is not a consistent finding. In recent research, Rostami et al. (2020) reported no differences

between the ADHD-C and ADHD-I subtypes with respect to internalizing problems, such as anxiety. Overall, individuals with an ADHD-C diagnosis seem to have the most severe difficulties among the subtypes, including more severe externalizing behaviours (Gaub & Carlson, 1997; Graetz et al., 2001; Wheeler & Carlson, 2000).

1.3 Peer victimization and ADHD subtypes

Peer victimization, otherwise known as bullying, is a form of relational aggression and can be described as the maltreatment, abuse, or neglect of a child or youth at the hands of another (Teicher et al., 2018; Wiener & Mak, 2009). Encompassed under the umbrella term, peer victimization are different forms of aggression: physical, verbal and relational (Wiener & Mak, 2009). As such, behaviours such as slapping, punching, kicking, name-calling, teasing, making threats, excluding, and rumour spreading, among many others, are all forms of peer victimization (Wiener & Mak, 2009). Peer victimization is a serious issue related to increased rates of suicidal ideation and suicide attempts in children, higher rates of youth mental health disorders, and higher rates of depression and anxiety disorders in adulthood. (Lereya et al., 2015; Sumter et al., 2015; Takizawa et al., 2014). Understanding the impact of peer victimization on psychosocial development is of increasing importance as more children have continuous access to technology and social media platforms, where forms of victimization such as threats, name calling, and teasing and harassment, can continue outside of school and reach children and youth in their homes (Sumter et al., 2015).

As a result of the increased frequency at which they experience peer victimization, children and youth with ADHD are often socially withdrawn and lack long-term friendships that have been demonstrated to serve as a protective factor and mitigate the negative effects associated with peer victimization (Cardoos & Hinshaw, 2011; Frankel & Feinberg, 2002;

Humphrey et al., 2007). Recent research has demonstrated that specific ADHD symptomatology is related to levels of peer victimization (Winters et al., 2020). In the study by Winters et al (2020), high levels of hyperactivity-impulsivity were associated with increased levels of peer victimization that remained high over time. Findings suggests that subtypes ADHD-H and ADHD-C are specifically at an elevated risk of peer victimization compared to the ADHD-I population.

1.4 ADHD, peer victimization and hippocampal morphology

Children with ADHD have been observed to differ from TD children in their brain morphology, however there are inconsistencies in the literature when comparing the hippocampal structure in ADHD to TD children (Harms et al., 2013; Hoogman et al. 2017; Perlov et al., 2008; Plessen et al., 2006; Posner et al., 2014; Shaw et al., 2017). Some studies have reported no difference in hippocampal volumes between ADHD and TD groups (Perlov et al., 2008), some have reported findings of decreased hippocampal volumes in ADHD (Posner et al., 2014), and other studies have reported increased hippocampal volumes in ADHD (Plessen et al., 2006). One theory that emerges from the literature is that the atypical brain structure often associated with ADHD may partially be related to the elevated levels of stress that are associated with the adversity, peer victimization and other types of early life stress, that are experienced at higher rates by children with ADHD (Humphreys et al., 2019b).

The hippocampus is a brain region of interest in relation to peer victimization and the broader adversity literature. Firstly, the hippocampus plays a major role in modulating the body's hormonal response to stress, and secondly, it is composed of stress-sensitive subregions like the Cornu Ammonis 3 (CA3) and the Dentate Gyrus (DG) (Dahmen et al., 2018; Keresztes et al., 2020; Sapolsky, 2000). Some evidence suggests that higher levels of adversity are associated

with smaller hippocampal volumes (Hanson et al., 2015; Humphreys et al., 2019a; Rao et al., 2010). In contrast, some studies find no relationship exists between adversity and hippocampal volumes (McLaughlin et al., 2014), and some studies in pediatric maltreatment-related PTSD populations have reported larger hippocampal volumes (Tupler & De Bellis, 2006).

Few studies have examined the relationship between peer victimization, as a particular form of adversity, and hippocampal volume. A recent study by Quinlan et al. (2018) used MRI to examine how self-reported peer victimization influenced brain morphology in a large sample of 682 TD adolescents. The researchers did not find any relationship between peer victimization and hippocampal volume; however, they did find that greater levels of peer victimization were related to larger putamen volumes in 14-year-olds (Quinlan et al., 2018). In a group of 31 TD male adolescents, Lee et al. (2018) reported that those who experienced verbal victimization, from both their peers and adults, had decreased left hippocampal volumes, particularly in the left Cornu Ammonis 1 (CA1) subfield and left subiculum. In a study by Teicher et al. (2018), peer physical abuse during childhood was inversely correlated with hippocampal volume in female but not male adults. To our knowledge, no studies have examined the relationship between hippocampal volume and peer victimization in ADHD.

There are various mechanisms that can explain the process by which hippocampal volumes might be increased or decreased. Firstly, during periods of significant stress glucocorticoids (GCs) are released by the adrenal gland and some evidence suggests that GCs kill neurons, causing decreased volumes in the hippocampus (Sapolsky, 2000). This was observed in rodent and primate models in the CA3 subfield of the hippocampus (Sapolsky, 2000). Contrarily, hyposensitization might occur with chronically elevated levels of stress in childhood and adolescence that can render the neurotoxic effects of the GCs ineffective, leading

to increased or unaltered hippocampal volumes (Janiri et al., 2019; Liberzon & Abelson, 2016; Sapolsky, 2000). Increased hippocampal volumes could also serve as a compensatory mechanism, for example in response to the presence of ADHD symptoms, as some research has found a larger hippocampal volume to be associated with lower levels of externalizing symptomatology (Plessen et al., 2006).

1.5 Hippocampal morphology and working memory

Executive functions help individuals organize and integrate basic functions to perform goal-oriented behaviours (Friedman & Miyake, 2017). The prefrontal cortex is often associated with executive function, although other brain areas are implicated, for example, the hippocampus, in conjunction with the prefrontal cortex, plays a large role in WM function (Friedman & Miyake, 2017; Harms et al., 2013). Based on a model developed by Baddeley in 1986, WM is thought to be composed of verbal and spatial stores, that enable information to be held in the short-term, and a central executive component that allows the information to be used and manipulated in real-time; for example in reading comprehension (as cited in Martinussen et al., 2005). WM deficits are often seen in children and adolescents with an ADHD diagnosis (Harms et al., 2013; Martinussen et al., 2005). The relationship between hippocampal volume and WM ability, however, is unclear for both ADHD and TD child and adolescent populations.

Neuronal loss in the hippocampus related to stress and elevated GCs has been linked to deficits in memory abilities (Sapolsky, 2000). A meta-analysis of TD populations indicated that larger brain volumes positively predicted intelligence, which included measures of WM (McDaniel, 2005; Sapolsky, 2000). In a study conducted with children who had experienced early adversity in the form of low birth weight, smaller hippocampal volumes were related to deficits in WM (Beauchamp et al., 2008). Contrarily, some studies involving children and

adolescents have reported a negative relationship between hippocampal volumes and WM, contrary to the typical pattern seen in adult and aging populations (Van Petten, 2004).

1.6 The current study

Peer victimization is of specific interest in the child and youth ADHD population due to their inattentive and/or hyperactive-impulsive symptoms. In turn, specific diagnosis subtypes, including ADHD-C and ADHD-H might be the most at-risk due to their hyperactivity-impulsivity symptomatology and engagement in problem behaviours such as rule breaking and aggression (Blake et al., 2016; Frankel & Feinberg, 2002; Winters et al., 2020). Evidence suggests that adversity is associated with altered brain development in pediatric populations with ADHD; however, in this complex population, the research is lacking in the area of peer victimization and its association with the hippocampus. Further, there is a lack of consensus about the downstream effects of peer victimization, brain development and its association with cognitive ability.

The current study will explore the incidence of social difficulties, including peer victimization, in children with ADHD compared to TD children, the association with hippocampal subfield development and subsequent cognitive ability. Specifically, the first aim was to examine how problem behaviours, including aggression, rule breaking, withdrawal, and social problems, and levels of peer victimization differ in TD children from those with different ADHD subtypes. We predicted that children and youth with ADHD would experience higher levels of all problem behaviours and higher levels of peer victimization compared to controls and that the ADHD-C group would have the highest levels of impairment. Our second aim was to examine whether hippocampal subfield volume could predict levels of problem behaviours and peer victimization in TD and ADHD subtype populations. We predicted that smaller

hippocampal subfield volumes would predict more severe problem behaviour and higher levels of peer victimization. The third aim was to examine if hippocampal subfield volumes were associated with WM abilities in TD and ADHD children. We predicted that larger hippocampal subfield volumes would predict better WM performance.

1.7 References

- American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5®)*. American Psychiatric Pub.
- Beauchamp, M. H., Thompson, D. K., Howard, K., Doyle, L. W., Egan, G. F., Inder, T. E., & Anderson, P. J. (2008). Preterm infant hippocampal volumes correlate with later working memory deficits. *Brain*, *131*(11), 2986-2994.
- Biederman, J., & Faraone, S.V. (2005). Attention-deficit hyperactivity disorder. *The Lancet*, *366*(9481), 237-248.
- Björkenstam, C., Jablonska, B., Dalman, C., & Kosidou, K. (2017). Cumulative exposure to childhood adversity, and treated Attention Deficit/Hyperactivity Disorder. *European Journal of Public Health*, *27*(suppl_3).
- Blake, J. J., Kim, E. S., Lund, E. M., Zhou, Q., Kwok, O. M., & Benz, M. R. (2016). Predictors of bully victimization in students with disabilities: A longitudinal examination using a national data set. *Journal of Disability Policy Studies*, *26*(4), 199-208.
- Brown, N. M., Brown, S. N., Briggs, R. D., Germán, M., Belamarich, P. F., & Oyeku, S. O. (2017). Associations between adverse childhood experiences and ADHD diagnosis and severity. *Academic Pediatrics*, *17*(4), 349-355.
- Cardoos, S. L., & Hinshaw, S. P. (2011). Friendship as protection from peer victimization for girls with and without ADHD. *Journal of Abnormal Child Psychology*, *39*(7), 1035-1045.
- Dahmen, B., Puetz, V. B., Scharke, W., von Polier, G. G., Herpertz-Dahlmann, B., & Konrad, K. (2018). Effects of early-life adversity on hippocampal structures and associated HPA axis functions. *Developmental Neuroscience*, *40*(1), 13-22.

- Deotto, A., Eastwood, J. D., & Toplak, M. E. (2021). Temperament Profiles Associated with Internalizing Symptoms and Externalizing Behavior in Adolescents with ADHD. *Child Psychiatry & Human Development*, 1-15.
- Foley, M. (2011). A comparison of family adversity and family dysfunction in families of children with attention deficit hyperactivity disorder (ADHD) and families of children without ADHD. *Journal for Specialists in Pediatric Nursing*, 16(1), 39-49.
- Frankel, F., & Feinberg, D. (2002). Social problems associated with ADHD vs. ODD in children referred for friendship problems. *Child Psychiatry and Human Development*, 33(2), 125-146.
- Friedman, N. P., & Miyake, A. (2017). Unity and diversity of executive functions: Individual differences as a window on cognitive structure. *Cortex*, 86, 186-204.
- Gaub, M., & Carlson, C. L. (1997). Behavioral characteristics of DSM-IV ADHD subtypes in a school-based population. *Journal of Abnormal Child Psychology*, 25(2), 103-111.
- Graetz, B. W., Sawyer, M. G., Hazell, P. L., Arney, F., & Baghurst, P. (2001). Validity of DSM-IV ADHD subtypes in a nationally representative sample of Australian children and adolescents. *Journal of the American Academy of Child & Adolescent Psychiatry*, 40(12), 1410-1417.
- Hanson, J. L., Nacewicz, B. M., Sutterer, M. J., Cayo, A. A., Schaefer, S. M., Rudolph, K. D., ... & Davidson, R. J. (2015). Behavioral problems after early life stress: contributions of the hippocampus and amygdala. *Biological Psychiatry*, 77(4), 314-323.
- Harms, M. P., Wang, L., Csernansky, J. G., & Barch, D. M. (2013). Structure–function relationship of working memory activity with hippocampal and prefrontal cortex volumes. *Brain Structure and Function*, 218(1), 173-186.

- Hoogman, M., Bralten, J., Hibar, D. P., Mennes, M., Zwiers, M. P., Schweren, L. S., ... & de Zeeuw, P. (2017). Subcortical brain volume differences in participants with attention deficit hyperactivity disorder in children and adults: a cross-sectional mega-analysis. *The Lancet Psychiatry*, *4*(4), 310-319.
- Humphrey, J. L., Storch, E. A., & Geffken, G. R. (2007). Peer victimization in children with attention-deficit hyperactivity disorder. *Journal of Child Health Care*, *11*(3), 248-260.
- Humphreys, K. L., King, L. S., Sacchet, M. D., Camacho, M. C., Colich, N. L., Ordaz, S. J., ... & Gotlib, I. H. (2019a). Evidence for a sensitive period in the effects of early life stress on hippocampal volume. *Developmental Science*, *22*(3), e12775.
- Humphreys, K. L., Watts, E. L., Dennis, E. L., King, L. S., Thompson, P. M., & Gotlib, I. H. (2019b). Stressful life events, ADHD symptoms, and brain structure in early adolescence. *Journal of Abnormal Child Psychology*, *47*(3), 421-432.
- Janiri, D., Sani, G., De Rossi, P., Piras, F., Banaj, N., Ciullo, V., ... & Spalletta, G. (2019). Hippocampal subfield volumes and childhood trauma in bipolar disorders. *Journal of Affective Disorders*, *253*, 35-43.
- Keresztes, A., Raffington, L., Bender, A. R., Bögl, K., Heim, C., & Shing, Y. L. (2020). Hair cortisol concentrations are associated with hippocampal subregional volumes in children. *Scientific Reports*, *10*(1), 1-12.
- Lee, S. W., Yoo, J. H., Kim, K. W., Kim, D., Park, H., Choi, J., Teicher, M. H., & Jeong, B. (2018). Hippocampal subfields Vol. reduction in high schoolers with previous verbal abuse experiences. *Clinical Psychopharmacology and Neuroscience*, *16*(1), 46-56.

- Lereya, S. T., Copeland, W. E., Costello, E. J., & Wolke, D. (2015). Adult mental health consequences of peer bullying and maltreatment in childhood: two cohorts in two countries. *The Lancet Psychiatry*, 2(6), 524-531.
- Liberzon, I., & Abelson, J. L. (2016). Context processing and the neurobiology of post-traumatic stress disorder. *Neuron*, 92(1), 14-30.
- Martinussen, R., Hayden, J., Hogg-Johnson, S., & Tannock, R. (2005). A meta-analysis of working memory impairments in children with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, 44(4), 377-384.
- McDaniel, M. A. (2005). Big-brained people are smarter: A meta-analysis of the relationship between in vivo brain volume and intelligence. *Intelligence*, 33(4), 337-346.
- McLaughlin, K. A. (2016). Future directions in childhood adversity and youth psychopathology. *Journal of Clinical Child & Adolescent Psychology*, 45(3), 361-382.
- McLaughlin, K. A., Sheridan, M. A., Winter, W., Fox, N. A., Zeanah, C. H., & Nelson, C. A. (2014). Widespread reductions in cortical thickness following severe early-life deprivation: a neurodevelopmental pathway to attention-deficit/hyperactivity disorder. *Biological Psychiatry*, 76(8), 629-638.
- Perlov, E., Philipsen, A., van Elst, L. T., Ebert, D., Henning, J., Maier, S., ... & Hesslinger, B. (2008). Hippocampus and amygdala morphology in adults with attention-deficit hyperactivity disorder. *Journal of Psychiatry & Neuroscience: JPN*, 33(6), 509.
- Plessen, K. J., Bansal, R., Zhu, H., Whiteman, R., Amat, J., Quackenbush, G. A., ... & Hugdahl, K. (2006). Hippocampus and amygdala morphology in attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*, 63(7), 795-807.

- Polanczyk, G., De Lima, M. S., Horta, B. L., Biederman, J., & Rohde, L. A. (2007). The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *American Journal of Psychiatry*, *164*(6), 942-948.
- Posner, J., Siciliano, F., Wang, Z., Liu, J., Sonuga-Barke, E., & Greenhill, L. (2014). A multimodal MRI study of the hippocampus in medication-naive children with ADHD: what connects ADHD and depression? *Psychiatry Research: Neuroimaging*, *224*(2), 112-118.
- Quinlan, E. B., Barker, E. D., Luo, Q., Banaschewski, T., Bokde, A. L., Bromberg, U., ... & Garavan, H. (2018). Peer victimization and its impact on adolescent brain development and psychopathology. *Molecular psychiatry*, 1-11.
- Rao, U., Chen, L. A., Bidesi, A. S., Shad, M. U., Thomas, M. A., & Hammen, C. L. (2010). Hippocampal changes associated with early-life adversity and vulnerability to depression. *Biological Psychiatry*, *67*(4), 357-364.
- Rostami, M., Khosrowabadi, R., Albrecht, B., Pouretmad, H., & Rothenberger, A. (2020). ADHD subtypes: Do they hold beyond core symptoms? A multilevel testing of an additive model. *Applied Neuropsychology: Child*, 1-11.
- Sapolsky, R. M. (2000). Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. *Archives of General Psychiatry*, *57*(10), 925-935.
- Schmitz, M., Cadore, L., Paczko, M., Kipper, L., Chaves, M., Rohde, L. A., ... & Knijnik, M. (2002). Neuropsychological performance in DSM-IV ADHD subtypes: An exploratory study with untreated adolescents. *The Canadian Journal of Psychiatry*, *47*(9), 863-869.

- 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), 1040-1049.
- Shaw, P., Eckstrand, K., Sharp, W., Blumenthal, J., Lerch, J. P., Greenstein, D. E. E. A., ... & Rapoport, J. L. (2007). Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proceedings of the National Academy of Sciences, 104*(49), 19649-19654.
- Sumter, S. R., Valkenburg, P. M., Baumgartner, S. E., Peter, J., & Van der Hof, S. (2015). Development and validation of the multidimensional offline and online peer victimization scale. *Computers in Human Behavior, 46*, 114-122.
- Takizawa, R., Maughan, B., & Arseneault, L. (2014). Adult health outcomes of childhood bullying victimization: evidence from a five-decade longitudinal British birth cohort. *American Journal of Psychiatry, 171*(7), 777-784.
- Teicher, M. H., Anderson, C. M., Ohashi, K., Khan, A., McGreenery, C. E., Bolger, E. A., ... & Vitaliano, G. D. (2018). Differential effects of childhood neglect and abuse during sensitive exposure periods on male and female hippocampus. *Neuroimage, 169*, 443-452.
- Thapar, A., Cooper, M., Jefferies, R., & Stergiakouli, E. (2012). What causes attention deficit hyperactivity disorder? *Archives of Disease in Childhood, 97*(3), 260-265.
- Tupler, L. A., & De Bellis, M. D. (2006). Segmented hippocampal volume in children and adolescents with posttraumatic stress disorder. *Biological Psychiatry, 59*(6), 523-529.
- Van Petten, C. (2004). Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: review and meta-analysis. *Neuropsychologia, 42*(10), 1394-1413.

- Wheeler, Maedgen, J., & Carlson, C. L. (2000). Social functioning and emotional regulation in the attention deficit hyperactivity disorder subtypes. *Journal of Clinical Child Psychology, 29*(1), 30-42.
- Wiener, J., & Mak, M. (2009). Peer victimization in children with attention-deficit/hyperactivity disorder. *Psychology in the Schools, 46*(2), 116-131.
- Winters, R. R., Blake, J. J., & Chen, S. (2020). Bully victimization among children with attention-deficit/hyperactivity disorder: a longitudinal examination of behavioral phenotypes. *Journal of Emotional and Behavioral Disorders, 28*(2), 80-91.

Chapter 2

2 Experiment: Peer victimization and the association with hippocampal development and working memory in children with and without ADHD

2.1 Introduction

Attention Deficit Hyperactivity Disorder (ADHD) affects approximately 5% of the child and youth population worldwide and is characterized by symptoms of hyperactivity-impulsivity, and inattention (American Psychiatric Association [APA], 2013; Polanczyk et al., 2007). ADHD is further characterized into three diagnostic subtypes, including ADHD hyperactive-impulsive type (ADHD-H), ADHD inattentive type (ADHD-I), and ADHD combined type (ADHD-C), (APA, 2013; Gadow et al., 2004). ADHD-H is characterized by clinically elevated symptoms of hyperactivity-impulsivity. ADHD-I is characterized by clinically elevated symptoms of inattention. Children and youth with ADHD-C display both clinically elevated hyperactivity-impulsivity and inattention symptoms (APA, 2013).

Children with ADHD have deficits in social skills and often act inappropriately in social situations, such as being disruptive and intrusive, which make maintaining healthy peer relationships difficult (Frankel & Feinberg, 2002; Humphrey et al., 2007). These social difficulties make children with ADHD susceptible to peer victimization and research has suggested that children with ADHD experience the highest rates of peer victimization when compared to children with other disabilities such as Autism Spectrum Disorder (ASD), Oppositional Defiant Disorder (ODD), intellectual disabilities, learning disabilities, and physical disabilities (Blake et al., 2016; Frankel & Feinberg; Humphrey et al., 2007). However, recent research has demonstrated that the levels of peer victimization experienced by children with ADHD vary according to their diagnosis subtype, with symptoms of hyperactivity-impulsivity

centrally implicated as a factor that increases risk of experiencing higher levels of peer victimization (Winters et al., 2020). Children with more severe hyperactivity-impulsivity symptoms also tend to exhibit more problem behaviours, such as rule breaking and externalized aggression, which can negatively influence the ability to form healthy peer relationships (Frankel & Feinberg, 2002; Humphrey et al., 2007). This suggests that children and youth with ADHD-H and ADHD-C are more susceptible to experiencing peer victimization than those with ADHD-I. Peer relationships play an important role in child development, and victimization by peers, including verbal, emotional, and physical abuse, can be a significant and potentially traumatizing stressor in a young person's life (Teicher et al., 2018; Quinlan et al., 2018).

Children with ADHD differ in their brain structure compared to their TD counterparts (Shaw et al., 2007). However, for many brain regions, including the hippocampus, how the structure differs between ADHD and TD children is unclear (Harms et al., 2013; Hoogman et al. 2017; Perlov et al., 2008; Plessen et al., 2006; Posner et al., 2014). In some studies, enlarged hippocampal volumes are reported in ADHD children compared to TD children, some studies report decreased hippocampal volumes in ADHD compared to TD children, and others report no differences (Hoogman et al. 2017; Perlov et al., 2008; Plessen et al., 2006; Posner et al., 2014).

The hippocampus is a structure of particular interest in the adversity literature because it is involved in regulating hormonal stress responses and is composed of stress-sensitive subfields including the Cornu Ammonis 1 (CA1), Cornu Ammonis 3 (CA3), and Cornu Ammonis 4 (CA4) (Dahmen et al., 2018; Sapolsky, 2000). It is also of particular interest of study in the ADHD population, considering children with ADHD are at an increased risk of experiencing chronic stress, including that related to peer victimization. (Hoogman et al. 2017; Perlov et al., 2008; Plessen et al., 2006; Posner et al., 2014).

Chronic stress has been hypothesized to impact the hippocampus in different ways. For one, during periods of increased stress, the adrenal gland releases glucocorticoids (GCs) (Sapolsky, 2000). In rodent and primate models, GCs have been observed to kill neurons in stress-sensitive subfields of the hippocampus, for example in the CA3, thereby leading to decreased volumes (Sapolsky, 2000). Other research suggests that chronically elevated levels of stress might lead to a reduced hormonal stress responsivity that can mitigate the neurotoxic effects of GCs, resulting in unaltered or even enlarged hippocampal volumes (Janiri et al., 2019; Liberzon & Abelson, 2016; Sapolsky, 2000). In the literature, both decreased and enlarged hippocampal volumes have been observed. Some studies have demonstrated that early life stress is associated with decreased hippocampal volumes, although in some pediatric populations, such as in children with maltreatment-related PTSD, larger hippocampal volumes have been observed in relation to increased adversity (Dahmen et al., 2018; Humphreys et al., 2019; Tupler & De Bellis, 2006).

The research on peer victimization as a form of early life stress and its association with hippocampal volume is scarce. In some studies, smaller hippocampal volumes were found in TD children who reported more peer victimization, but further research is required to obtain a better understanding of this relationship (Lee et al., 2018; Quinlan et al., 2018). Further, the association between peer victimization to hippocampal volume in the ADHD population and how this differs between ADHD subtypes has not been studied.

In addition to its involvement in regulating the stress response, the hippocampus is also a key structure in executive functioning (McDaniel, 2005). In adult and aging populations, larger hippocampal volumes are associated with better performance on tasks of executive functioning, including working memory (WM) (Beauchamp et al., 2008; McDaniel, 2005; Van Petten, 2004).

However, this same relationship is not consistently observed in children, with some evidence suggesting that children with larger hippocampal volumes perform worse on tasks of memory (Van Petten, 2004). Children with ADHD exhibit deficits in WM, however the relationship between hippocampal volume and WM ability in the ADHD population remains largely unexplored (Martinussen et al., 2005).

In the current work, we examined the association amongst social difficulties, brain development and executive function in a large heterogenous sample of children with ADHD and TD children. We addressed three main research questions: 1) Are problem behaviours and peer victimization predicted by ADHD diagnostic category? 2) Do hippocampal subfield volumes predict problem behaviours and peer victimization levels? 3) Do hippocampal subfield volumes predict WM ability? Our central hypothesis is that ADHD participants will report higher levels of problem behaviours and peer victimization compared to TD children, and that hippocampal subregion volumes will significantly predict levels of peer victimization as well as WM ability.

2.2 Methods

2.2.1 Participants

Participants in this study ranged in age from 6.00 to 17.70 years. Data were collected by researchers at the Child Mind Institute and participants were recruited as part of the Healthy Brain Network initiative (Alexander et al., 2017). Both typically developing (TD) participants and those with a clinical diagnosis of ADHD were tested at three sites: Rutgers University, Citigroup Biomedical Imaging Center, and Staten Island Diagnostic Research Center, all in New York. The research ethics boards at all respective institutions approved the study. Written informed consent was obtained from the participants' parents and written assent was obtained from the participants. A breakdown of participant demographics can be found in Table 1.

Table 1. Characteristics of TD, ADHD-C and ADHD-I participants.

	TD n= 218	ADHD-C n= 108	ADHD-I n= 124
Age, years,	9.80	8.80	10.60
Median [IQR]	[7.90-12.72]	[7.26-11.24]	[8.58-13.05]
Male, % (n)	50.5 (110)	79.6 (86)	75.8 (94)
MRI Site, % (n)†			
CBIC	14.2 (31)	25.0 (27)	27.0 (34)
RU	34.9 (76)	31.5 (34)	47.6 (59)
SI	26.1 (57)	16.7 (18)	5.60 (7)
Unknown	0.9 (2)	0 (0)	0 (0)
BSMSS Total,	53.00	53.00	53.00
Median [IQR]	[46.00-61.00]	[44.88-61.00]	[45.00-59.50]
SWAN, Median [IQR]			
Hyperactivity-Impulsivity	-0.11 [-1.42-0.22]	1.11 [0.67-1.67]	0.22 [0.00-0.67]
Inattention	-0.06 [-1.22-0.44]	1.11 [0.67-1.67]	1.22 [0.56-1.89]
CBCL, Median [IQR]			
Aggressive Behaviour	3.00 [0.00-5.00]	8.00 [4.25-13.00]	4.00 [1.00-8.00]
Rule Breaking Behaviour	1.00 [0.00-2.00]	3.00 [1.00-5.00]	2.00 [0.00-3.00]
Social Problems	1.00 [0.00-3.00]	3.50 [1.00-6.00]	2.00 [0.00-3.75]

Withdrawn	1.00 [0.00-2.00]	1.00 [0.00-3.00]	1.00 [0.00-3.00]
Peer Victimization	0.00 [0.00-0.00]	1.00 [0.00-2.00]	0.00 [0.00-1.00]
WISC-V, Median [IQR]			
FSIQ	106.00 [95.00-113.00]	105.00 [91.75-113.00]	99.00 [88.00-109.00]
WMI	100.00 [91.00-112.00]	100.00 [91.00-110.00]	94.00 [88.00-107.00]
TCV (mm ³)			
Median [IQR]	1176718.50 [1104748.00- 1268853.75]	1202310.00 [1104571.00- 1260378.00]	1217219.00 [1142320.00- 1334728.00]
Left CA3 (mm ³),			
Median [IQR]	178.68 [162.48-199.21]	178.74 [165.64-203.56]	200.11 [182.77-216.74]
Left CA4 (mm ³),			
Median [IQR]	234.68 [215.67- 255.58]	233.00 [218.29-252.00]	250.05 [230.20-268.30]

Clinical and demographic factors: IQR, interquartile range; CBIC, Citigroup Biomedical Imaging Center; RU, Rutgers University; SI, Staten Island Diagnostic Research Center; BSMSS, Barratt Simplified Measure of Social Status; SWAN, Strengths and Weaknesses Assessment of ADHD and Normal Behaviour; CBCL, Child Behaviour Checklist; TCV, total cerebral volume; Left CA3, Cornu Ammonis 3; WISC-V, Wechsler Intelligence Scale for Children-v; FSIQ, Full Scale IQ; WMI, Working Memory Index. †MRI site used as covariate in aims 2 and 3.

In combination with clinical judgment, the computerized version of the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS-COMP) was administered under the supervision of a licensed clinician to make diagnoses of ADHD, and to confirm the absence of ADHD diagnoses in TD participants (Kaufman et al., 1997). Participants diagnosed with ADHD were further divided into subgroups, those diagnosed with ADHD-I and those diagnosed with ADHD-C. Participants with an ADHD-H diagnosed were excluded from this study due to a small sample size of only 15 participants having received this subtype diagnosis. All participants in the study were fluent in English, had a parent that was able to complete informant questionnaires, had an Intelligence Quotient (IQ) score of over 66, and were free of brain injury or disease. Participants were excluded if they presented with schizophrenia or bipolar disorder, psychosis, substance dependence, acute intoxication, a neurodegenerative disorder, or any other neurodevelopmental disorder.

2.2.2 Procedures

The data for this study was collected in 4 study visits. In the first visit, the WISC-V was administered by a trained psychometrist. The second visit consisted of the MRI protocol, including the T1 sequence conducted by a trained MRI technician. During the scan participants watched two cartoon movies, the first movie was a short-film titled ‘The Present’ and the second was a 10-minute clip from the full-length film ‘Despicable Me.’ Parent questionnaires were completed during the third visit and K-SADS-COMP was completed during the fourth and final visit.

2.2.3 Demographic Measures

The Barratt Simplified Measure of Social Status (BSMSS) was used as a measure of socioeconomic status (SES) and was completed by a parent (Barratt, 2006). The BSMSS

assesses level of education and occupation for both of a child's parents, or from one parent if the child is from a single-parent household (Barratt, 2006). The scores were converted into a total score between 8-66 for each child, with a higher score indicative of a higher SES (Barratt, 2006).

2.2.4 Psychological Measures

To assess symptoms of hyperactivity-impulsivity and inattention, the Strengths and Weaknesses Assessment of ADHD and Normal Behaviour (SWAN) was completed by a parent (Swanson et al., 2001). To measure levels of problem behaviours in the participants, the Child Behaviour Checklist (CBCL) was administered to parents (Achenbach, 1991). The subscales used from the CBCL in this study included the aggressive behaviour, rule breaking behaviour, social problems and withdrawn scales. In addition, peer victimization was measured using the CBCL subscale developed by McCloskey and Stuewig (2001), comprised of four questions: "doesn't get along with other kids", "gets in many fights", "gets teased a lot", and "not liked by other children." The Wechsler Intelligence Scale for Children-fifth edition (WISC-V) was used to obtain a Working Memory Index (WMI) in all participants, including a digit span task and a picture span task (Wechsler, 2014).

2.2.5 Magnetic Resonance Imaging

A Siemens 3T Trio scanner was used at the Rutgers University site (Alexander et al., 2017). At the Staten Island Diagnostic Research Center, participants were scanned on a 1.5T Siemens Avanto scanner and at Citigroup Biomedical Imaging Center participants were scanned on a Siemens 3T Prisma. To adjust for the differences in scanners, statistical models included Magnetic Resonance Imaging (MRI) site as a covariate.

High-resolution anatomical images were acquired using a 3D-MPRAGE pulse sequence with 192 T1-weighted, straight sagittal slices (1 mm thickness).

2.2.6 Hippocampal Segmentation

To obtain hippocampal subfield volumes from the structural images, FreeSurfer (<http://surfer.nmr.mgh.harvard.edu>) version 6.0. was used to segment and isolate hippocampal structures at high-resolution (Iglesias et al., 2015). The hippocampus was segmented, bilaterally, into the hippocampal tail, subiculum, CA1, hippocampal fissure, presubiculum, parasubiculum, molecular layer, granule cell layers of the dentate gyrus (GCMLDG), CA3, CA4, fimbria, and the hippocampus-amygdala-transition-area (HATA). The total cerebral volumes were extracted using the Freesurfer pipeline.

2.2.7 Statistical Analysis

Statistical analyses were completed the IBM SPSS Statistics software package (version 26, Statistical Package for the Social Sciences, IBM, Armonk, NY).

Our first aim was to examine problem behaviour and peer victimization in children and adolescents with TD, ADHD-I, ADHD-C. In five general linear models, we examined parent-reported problem behaviours and peer victimization (social problems, aggressive behaviour, rule breaking behaviour, withdrawal and peer victimization subscale raw scores; dependent variables) in related to diagnostic group (TD, ADHD-I, ADHD-C; independent variables). Age, sex, socioeconomic status (using the BSMSS), and study site/MRI site were adjusted for in each model.

Our second aim was to examine problem behaviour and peer victimization and their relationships to hippocampal subfield volume. In four general linear models we examined peer victimization (subscale raw score; dependent variable), aggressive behaviour (subscale raw score; dependent variable), rule breaking behaviour (subscale raw score; dependent variable), and social problems (subscale raw score; dependent variable) in relation to hippocampal subfield

volumes (right and left hippocampal tail, subiculum, CA1, hippocampal fissure, presubiculum, parasubiculum, molecular layer, GCMLDG, CA3, CA4, fimbria and HATA; independent variables), while adjusting for age, sex, socioeconomic status (using the BSMSS), diagnostic group, total cerebral volume (TCV), and MRI site.

Our third aim was to examine the association of hippocampal subfield volumes and working memory ability. A general linear model was used to examine the relationship between the left and right hippocampal subfield volumes (hippocampal tail, subiculum, CA1, hippocampal fissure, presubiculum, parasubiculum, molecular layer, GCMLDG, CA3, CA4, fimbria and HATA; independent variables), and working memory ability (WISC-V: working memory subscale standardized score; dependent variable). We adjusted for age, sex, socioeconomic status (using the BSMSS), diagnostic group, TCV, and MRI site.

2.3 Results

2.3.1 Participant Demographics

A total of 218 TD participants (median age = 9.80 years; 50.5% male) and 232 participants diagnosed with ADHD (median age=9.82 years; 77.6% male) were recruited. Of the 232 children and adolescents diagnosed with ADHD, 108 participants had the ADHD-C subtype (median age = 8.80 years; interquartile range [IQR] = 7.26-11.24 years; 79.6% male) and 124 participants had the ADHD-I subtype (median age = 10.60 years; IQR = 8.58- 13.05 years; 75.8% male). Participant characteristics can be found in Table 1.

2.3.2 Problem Behaviours, Peer Victimization and Diagnostic Group

In our first aim, we examined the relationship between problem behaviours from the CBCL, including social problems, rule breaking behaviour and aggressive behaviour, and diagnostic group (TD, ADHD-I, and ADHD-C). We also examined how the experience of peer

victimization differs by diagnostic group (TD, ADHD-I, and ADHD-C). Age, sex, SES, and study site were adjusted for in all the models. In the problem behaviours models 433 participants were included in analysis, 204 TD children, 123 ADHD-I children, and 106 ADHD-C children. Seventeen participants were excluded from the problem behaviour analyses due to missing data. In the peer victimization model a total of 431 total participants were included in the analysis, 203 TD children, 123 ADHD-I children, and 105 ADHD-C children.

Compared to the TD group, children and adolescents from both the ADHD-C ($B=5.42$, $95\%CI=4.26-6.58$, $p<0.001$) and ADHD-I ($B=2.41$, $95\%CI=1.32-3.51$, $p<0.001$) groups had significantly higher scores on the aggressive behaviour subscale. ADHD-C participants also had significantly higher scores than the TD participants on the rule breaking behaviour ($B=1.95$, $95\%CI=1.39-2.50$, $p<0.001$) and social problems ($B=2.16$, $95\%CI=1.53-2.78$, $p<0.001$) subscales. No significant differences were found between the TD and ADHD-C participants on the withdrawn ($B=0.51$, $95\%CI=0.03-0.99$, $p=0.038$) subscale. Nor were significant differences found between the TD and ADHD-I participants on the rule breaking behaviour ($B=0.62$, $95\%CI=0.10-1.15$, $p=0.021$), social problems ($B=0.75$, $95\%CI=0.16-1.33$, $p=0.013$), or withdrawn ($B=0.49$, $95\%CI=-0.04-0.94$, $p=0.033$) subscales. In comparing ADHD-C to ADHD-I children, we found that the ADHD-C children had significantly higher scores on aggressive behaviour, rule breaking behaviour, and social problems (all, $p<0.001$).

When examining the peer victimization subscale, children with ADHD-C had significantly higher levels of peer victimization compared TD children ($B=0.73$, $95\%CI=0.47-0.98$, $p<0.001$), but there was no significant difference found for peer victimization between the ADHD-I and TD groups ($B=0.09$, $95\%CI=-0.16-0.33$, $p=0.483$). In addition, the ADHD-C

children had significantly higher peer victimization scores than the ADHD-I children ($p < 0.001$).

Refer to Figure 1 for a summary of the results.

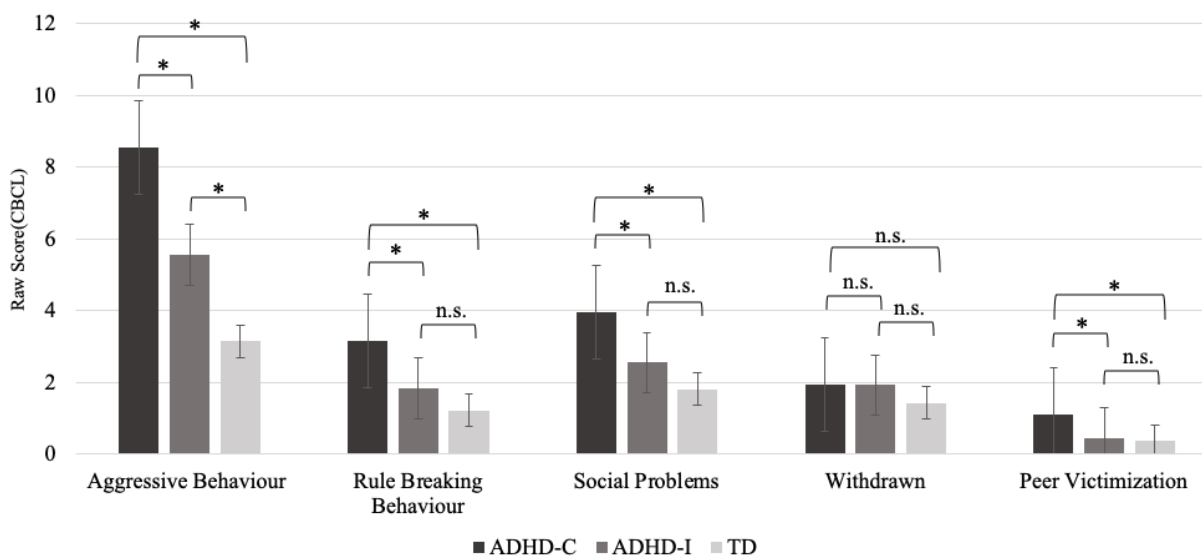


Figure 1. Problem Behaviours and Peer Victimization in Diagnostic Groups. CBCL subscale scores for children and adolescents from the ADHD-C, ADHD-I, and TD groups. Children and adolescents from the ADHD-C group had significantly higher Aggressive Behaviour, Rule Breaking Behaviour, Social Problems, and Peer Victimization scores compared to the TD group. The ADHD-C group also had significantly higher Aggressive Behaviour, Rule Breaking Behaviour, Social Problems and Peer Victimization scores compared to the ADHD-I group. Children and adolescents in the ADHD-I group had significantly higher Aggressive Behaviour scores than the TD group. None of the groups significantly differed on the Withdrawn scores. Scores represent the estimated marginal means, adjusted for age, sex, study site, and SES. P values are Bonferroni corrected (pairwise) for multiple comparisons. Error bars reflect standard error. * $p < 0.001$

2.3.3 Problem Behaviours, Peer Victimization and Hippocampal Subfield Volumes

In our second aim, we examined whether hippocampal subfield volumes could predict problem behaviours and levels of peer victimization. The problem behaviours examined in this aim included aggressive behaviour, rule breaking behaviour, and social problems subscales, adjusting for age, sex, SES, MRI site, diagnostic group, and TCV. The analysis was run with a total of 282 participants, including 136 TD children, 83 ADHD-I children, and 63 ADHD-C children.

Left CA3 volume was positively associated with peer victimization ($B=0.019$, 95% CI= 0.005-0.034, $p=0.010$). Left CA3 volume showed a positive but not-significant association with rule breaking behaviour ($B=0.034$, 95% CI=0.003-0.066, $p=0.032$), aggressive behaviour ($B=0.054$, 95% CI=-0.010 – 0.119, $p=0.097$), and social problems ($B=0.029$, 95% CI=-0.006-0.064, $p=0.107$).

We subsequently examined the interaction between left CA3 volume and diagnostic group (left CA3 volume x diagnostic group) in the peer victimization model. We found that left CA3 volume was significantly and positively associated with peer victimization in TD children ($B=0.018$, 95% CI=0.003-0.33, $p=0.017$), ADHD-C children ($B=0.022$, 95% CI=0.007-0.036, $p=0.004$), and ADHD-I children ($B=0.017$, 95% CI=0.003-0.032, $p=0.022$).

2.3.4 Hippocampal Subfield Volumes and Working Memory Ability

This analysis included a total of 243 participants, including 109 TD children, 76 ADHD-I children, and 58 ADHD-C children. When adjusting for age, sex, SES, MRI site, TCV, and hippocampal subfield volumes the ADHD-I group had significantly poorer WM scores than the TD group ($B=-5.49$, 95% CI = -9.75- -1.23, $p=0.011$), but the ADHD-C group did not significantly differ from the TD group ($B=-4.31$, 95% CI= -8.95- 0.33, $p=0.069$).

We examined the relationship between hippocampal subfield volumes and WMI (WISC-V). Left CA3 volume was found to be significantly and positively associated with WMI ($B=0.233$, $95\%CI=0.042-0.424$, $p=0.017$). Statistical interactions were tested in the WMI model between left CA3 volume and diagnostic group (left CA3 x diagnostic group). Left CA3 volume was significantly and positively associated with WMI in TD children ($B=0.249$, $95\%CI=0.59-0.440$, $p=0.010$), ADHD-C children ($B=0.230$, $95\%CI=0.038-0.422$, $p=0.019$), and ADHD-I children ($B=0.220$, $95\%CI=0.30-0.411$, $p=0.023$).

Left CA4 volume was found to be significantly and negatively associated with WMI ($B=-0.626$, $95\%CI=-1.14- -0.107$, $p=0.018$). Statistical interactions were also tested in the WMI model between left CA4 and diagnostic group. Left CA4 volume was significantly and negatively associated with WM in TD children ($B=-0.608$, $95\%CI=-1.128- -0.089$, $p=0.022$), ADHD-C children ($B=-0.625$, $95\%CI=-1.141- -0.108$, $p=0.018$), and ADHD-I children ($B=-0.632$, $95\%CI=-1.151- -0.113$, $p=0.017$).

2.3.5 Post-Hoc Cluster Analysis

To examine the associations amongst diagnosis, hippocampal volumes, WM ability as well as ADHD symptomatology, a K-means cluster analysis was performed with 245 participants: 111 TD, 58 ADHD-C, and 76 ADHD-I. The analysis included variables of brain morphology, behaviour, and cognition (Z-scored). The model included, left CA3 volume ($p=0.018$), peer victimization score ($p<0.001$), WMI ($p<0.001$), and the hyperactivity-impulsivity and inattention subscales from the SWAN (both $p<0.001$). Refer to Table 2 for a summary of the clusters.

Table 2. Three-Cluster Model Participant Demographics.

	Cluster 1 n= 41	Cluster 2 n= 54	Cluster 3 n= 150	P value
Left CA3 (mm ³),	180.00	183.01	191.08	0.018
Median [IQR]	[155.82 – 196.24]	[169.90- 207.00]	[172.81- 211.52]	
WMI	107.00	100.00	97.00	
Median [IQR]	[98.50-122.00]	[88.00 – 110.00]	[88.00-104.00]	<0.001
Peer Victimization	0.00	2.00	0.00	<0.001
Median [IQR]	[0.00-0.00]	[2.00-3.25]	[0.00-0.00]	
SWAN				
Hyperactivity-Impulsivity	-1.22	0.72	0.22	<0.001
Median [IQR]	[-2.78- -0.56]	[0.22-1.44]	[0.00-0.78]	
Inattention	-1.56	1.00	0.78	<0.001
Median [IQR]	[-2.22 - -0.78]	[0.22-1.67]	[0.11-1.44]	

Clinical factors: SWAN, Strengths and Weaknesses Assessment of ADHD and Normal

Behaviour; CBCL, Child Behaviour Checklist; TCV, total cerebral volume; Left CA3, Cornu

Ammonis 3; WISC-V, Wechsler Intelligence Scale for Children-v; WMI, Working Memory

Index.

Cluster 1 included a total of 41 participants and is characterized as children with small left CA3 volumes, high WMI scores, low peer victimization scores, and low hyperactivity-impulsivity and inattention symptomatology scores. This group is made up of 40 TD participants, and 1 participant from the ADHD-I group. All but 3 participants in this cluster scored 0.5 SD below the mean on the peer victimization scale. In this cluster 56% of the participants had left CA3 volumes that were below the average and 75% of the participants had higher average WMI. In regard to symptoms of hyperactivity-impulsivity and inattention, 39% of the participants in cluster 1 scored 1 SD below the mean and 34% scored below 2 SD below the mean.

Cluster 2 included a total of 54 participants. Participants in this group have average left CA3 volumes, average WMI scores, high peer victimization scores, and high hyperactivity-impulsivity and inattention symptomatology. This group is made up of 19 TD participants, 24 ADHD-C participants and 11 ADHD-I participants. All participants in this cluster were above average in peer victimization scores, with approximately 41% of the cluster at least 2 SD above the mean, and 56% above 1 SD. In this cluster 54% of participants had left CA3 volumes that were below average and 20% of participants had WMI at least 1 SD below the average. In regard to symptomatology, 20% of the participants had hyperactivity-impulsivity scores at least 1 SD above the mean, and 28% had inattention scores at least 1 SD above the mean.

Cluster 3 included a total of 150 participants and can be described as participants with large left CA3 volumes, low WMI scores, low peer victimization scores, and average hyperactivity-impulsivity and inattention symptomatology. This cluster is made up of 52 TD participants, 34 ADHD-C participants, and 64 participants from the ADHD-I group. In cluster 3, approximately 79% of the participants had peer victimization scores that were 0.5 SD below the

mean, A total of 60% of the participants had left CA3 volumes that were above the mean, with 21% being least 1 SD above the average. Approximately 30% of this cluster had WMI above the mean, and most participants in this cluster were above average in hyperactivity-impulsivity and inattention symptomatology, 57% and 60% respectively.

When examining cluster membership by diagnostic groups, we found 36% of the total TD sample (n=111) was grouped into cluster 1, 17% were grouped into cluster 2, and 47% were grouped into cluster 3. Of the 58 total ADHD-C participants, 41% were grouped into cluster 2, and 59% were grouped into cluster 3. Of the 76 total ADHD-I participants, 1% belonged to cluster 1, 14% were grouped into cluster 2, and 84% were grouped into cluster 3. Refer to Figure 2 for a summary of the cluster analysis.

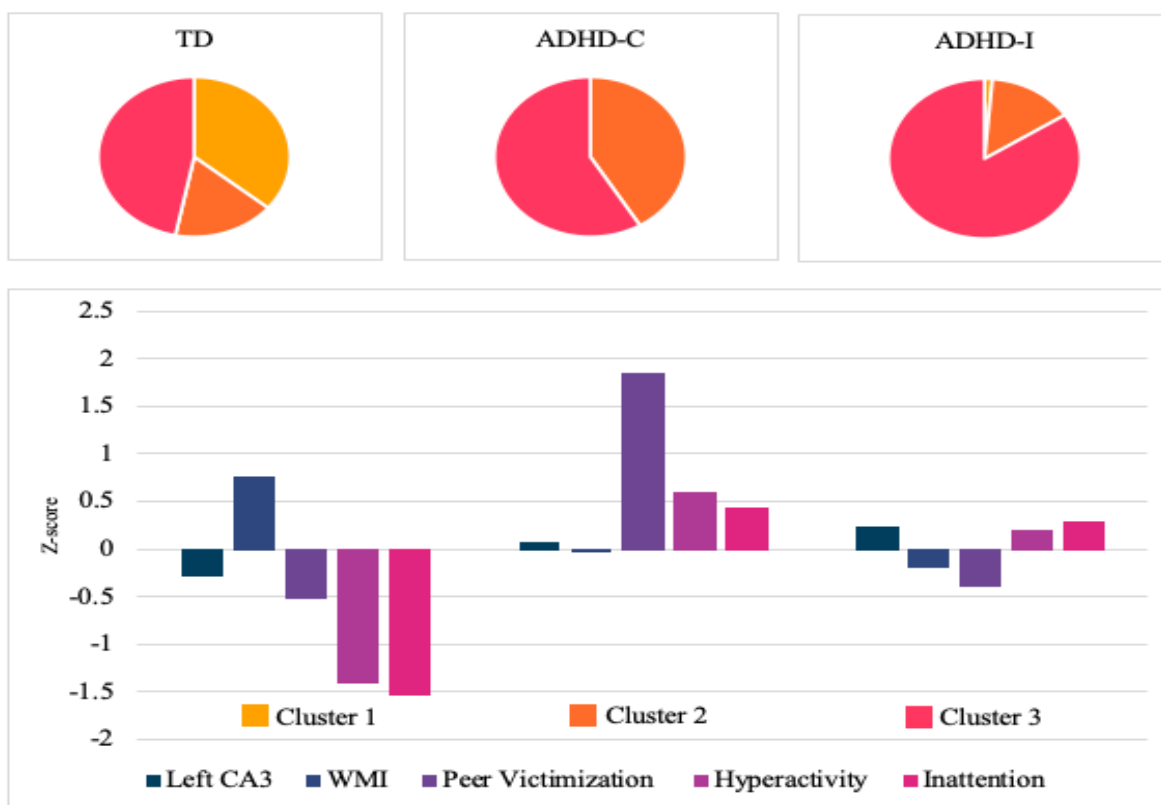


Figure 2. K-means Clustering based on Peer Victimization, Left CA3, WMI, Hyperactivity-Impulsivity and Inattention. The three-cluster model is depicted above. Cluster 1 is

characterized by small left CA3 volume, high WMI, low peer victimization, and low hyperactivity-impulsivity and inattention. Cluster 1 is almost entirely made up of TD participants. Cluster 2 is characterized as average left CA3 volumes, average WMI, high peer victimization, and high hyperactivity-impulsivity and inattention. Of the participants in cluster 2, 44% are from the ADHD-C group. Cluster 3 is characterized as large left CA3 volume, low WMI, low peer victimization, and average hyperactivity-impulsivity and inattention. Cluster 3 is approximately 43% ADHD-I participants, 35% TD participants, and 22% ADHD-C participants.

A one-way ANOVA was conducted to examine the differences between the clusters on all the variables. Significant between-group differences were found for all the variables: left CA3 volume ($F(2, 242)=4.07, p=0.018$), WMI ($F(2,242)=15.44, p<0.001$), peer victimization ($F(2,242)=364.86, p<0.001$), hyperactivity-impulsivity ($F(2,242)=103.63, p<0.001$), and inattention ($F(2,242)=112.24, p<0.001$). Post hoc multiple comparison using Bonferroni correction revealed the differences between the clusters. Significant differences were found between Cluster 1 and Cluster 2 on WMI, peer victimization, hyperactivity-impulsivity, and inattention (all $p<0.001$). Significant differences were found between Cluster 1 and 3 on Left CA3 volume ($p=0.015$), WMI, hyperactivity-impulsivity, and inattention (all $p<0.001$). Significant differences were found between Cluster 2 and 3 on peer victimization ($p<0.001$) and hyperactivity-impulsivity ($p=0.001$).

2.4 Discussion

The presence of problem behaviours, levels of peer victimization, hippocampal subfield morphology, and working memory were assessed in a large heterogenous sample of children and adolescents further divided by diagnostic group: TD, ADHD-C and ADHD-I. We found that problem behaviours and levels of peer victimization differed between TD, ADHD-C, and ADHD-I groups. We also report that hippocampal subfield volumes predict the presence of peer

victimization levels in children with ADHD and TD children. Lastly, hippocampal subfield volumes were associated with working memory ability in children with ADHD and TD children. Peer victimization was highest in children that displayed high levels of hyperactivity-impulsivity. Findings suggest that children with ADHD-C who display elevated levels of hyperactivity-impulsivity may be at greater risk for peer victimization.

2.4.1 Problem Behaviours, Peer Victimization and Diagnostic Group

As hypothesized, children in the ADHD diagnostic groups had elevated levels problem behaviours and peer victimization compared to TD children. Parents of children with ADHD-C reported higher levels of aggressive behaviour, rule breaking behaviour, social problems, and higher levels of experiencing peer victimization in their children compared to parental reports for TD and ADHD-I children. The ADHD-I children only differed from the TD children when comparing levels of aggressive behaviour; with significantly higher reported levels in the ADHD-I group. No significant differences were found in levels of withdrawal between any of the diagnostic groups.

Children and adolescents with ADHD are typically not well-liked by their peers and often experience social rejection and victimization (Humphrey et al., 2007). Children with ADHD who display more severe levels of externalizing behaviours have been observed to be the most at-risk pediatric population to experience peer victimization (Blake et al., 2016; Humphrey et al., 2007). Investigation into how peer victimization differs amongst the diagnosis subtypes of ADHD is sparse. Recent findings into the symptomatology of ADHD in relation to peer victimization suggest that more severe symptoms of hyperactivity-impulsivity are associated with higher rates of peer victimization among children (Winters et al., 2020). Not only are hyperactive-impulsive symptoms related to experiencing more victimization, it has also been demonstrated that

individuals with these symptoms are also more likely to also be perpetrators of bullying themselves (Winters et al., 2020). This notion is consistent with the findings from the present study. Although the peer victimization measure in the present study only accounted for experiencing victimization, the significantly elevated aggressive behaviour, rule breaking behaviour, and social problems scores in the ADHD-C group suggest that this group might also be perpetrators of victimization as well and might fit the profile of a bully victim (Winters et al., 2020). As the ADHD-I group has levels of hyperactivity-impulsivity that are comparable to the TD group, it follows that they are victimized by their peers at rates similar to the TD group. Although the ADHD-I children also had significantly elevated aggression scores compared to TD children, the lack of hyperactivity-impulsivity symptoms combined with low rates of peer victimization suggest that this group might fit into a different category than the ADHD-C group; that is, one of aggressive children and adolescents that are accepted by their peers (Farmer et al. 2010).

Experiencing peer victimization may be traumatizing, with a tremendous impact on later psychological development (Wolke et al., 2013). It is crucial that future research focuses on examining the impact of different types of victimization on child and adolescent psychological health. Determining how different types of victimization effect children can inform intervention strategies and can be useful for informing school-based interventions.

2.4.2 Hippocampal Subfield Volume, Problem Behaviours and Peer Victimization

In the current study, contrary to our hypothesis, larger left CA3 volumes were associated with higher parent-reported rates of peer victimization in children with ADHD-C, ADHD-I and TD children. The CA3 region is a particularly stress-sensitive area and has previously been associated with early life adversity (Teicher et al., 2012; Teicher et al., 2018). Typically, smaller

hippocampal volumes have been associated with a greater incidence of trauma and adversity in TD children (Dahmen et al., 2018; Sapolsky, 2000; Teicher et al., 2012). However, this association has been found to be different in children with mental health and neurodevelopmental disorders (Groen et al., 2010; Janiri et al., 2019; Tupler & De Bellis, 2006). Some models suggest that chronically elevated levels of stress during childhood may cause reduced stress responsivity which in turn may mitigate the neurotoxic effects GCs typically have in atrophying the neurons of the hippocampus (Janiri et al., 2019; Liberzon & Abelson, 2016; Sapolsky, 2000). This cascade of events results in larger hippocampal volumes, as found in our study.

Research conducted with pediatric post-traumatic stress disorder (PTSD) populations has provided evidence for larger hippocampal volumes when compared to matched non-traumatized groups, suggesting that anxiety and stress may be associated with increased growth of the hippocampus (Tupler & De Bellis, 2006). A recent study found larger subiculum, presubiculum, and CA1 volumes to be associated with childhood trauma in bipolar children (Janiri et al., 2019). Children with ASD have also been found to have enlarged hippocampal volumes compared to TD children (Groen et al., 2010), and larger hippocampal volumes in children with ADHD have also been observed (Plessen et al., 2006). Plessen et al. (2006) found hippocampal volumes to be inversely related to symptom severity in ADHD-C, whereas Tupler & De Bellis (2006) found larger hippocampal volumes to be associated with increased externalizing symptoms.

Future research in this area should focus on examining if and how the relationship between hippocampal volume and peer victimization differs according to gender and age. To maintain the large sample size in the current study we were not able to split our population in these ways; however, these factors were used as covariates. Age was not a significant covariate

in the model relating hippocampal volumes and peer victimization. In addition, future research is warranted in elucidating the relationship between ADHD subtype, symptomatology and peer victimization in relation to hippocampal volume, specifically in including the ADHD-H subtype.

2.4.3 Hippocampal Subfield Volume and Working Memory

The ADHD-I children had significantly lower scores on the WMI when compared to TD children. The ADHD-C group did not significantly differ from the ADHD-I group nor the TD group on WMI scores. Working memory deficits are often seen in children with an ADHD diagnosis (Martinussen et al., 2005; Ramos et al., 2020). However, there is a lack of consensus on how the different ADHD subtypes differ in respect to working memory ability, and cognitive ability in general. Some studies report no differences between high and low inattention symptoms and working memory scores (Jonkman et al., 2017). Other studies have found inattention to be a significant predictor of working memory ability in adolescents with ADHD (Rogers et al., 2011). As children with ADHD-C also have clinically elevated symptoms of inattention, it is unclear why the ADHD-C children did not display WM deficits when compared to the TD children in our study.

Larger left CA3 volumes and smaller left CA4 volumes were significantly predictive of higher WMI scores in all of the diagnostic groups. CA3 and CA4 are both key hippocampal subfields that are involved in WM (Voineskos et al., 2015). Larger volumes predict better cognitive function in adult samples (Beauchamp et al., 2008; McDaniel, 2005; Van Petten, 2004). Yet, findings in children and adolescents provide inconsistent results to support this view. In a meta-analysis by Van Petten (2004), multiple studies examining hippocampal volume and memory performance in child and adolescent populations found negative correlations between volume and memory abilities. This suggests that the positive relationship between cognitive

ability and hippocampal brain volume may increase with age (Van Petten, 2004). A recent study found that as children age, smaller hippocampal volumes are associated with superior memory abilities (Attila et al., 2020; Riggins et al., 2018). Previous studies examined whole hippocampal volumes. Future studies should investigate the relationship between hippocampal subfield volumes and working memory ability in ADHD populations.

2.4.4 ADHD Subtypes, Hippocampal volumes, Working memory and Peer Victimization

A three-cluster K-means model was used to characterize the present study population. Cluster 1 included 40 TD children and 1 child with ADHD-I who have low levels of inattentive and hyperactive-impulsive symptomatology, good working memory ability, and low peer victimization. Cluster 2 included 19 TD, 24 ADHD-C and 11 ADHD-I children who have significantly elevated levels of peer victimization and hyperactivity-impulsivity when compared to the two other clusters. Cluster 3 included 52 TD, 34 ADHD-C and 64 ADHD-I children who have significantly enlarged left CA3 volumes and significantly higher hyperactivity-impulsivity and WMIs compared to children in Cluster 1.

The results of the cluster analysis suggest that ADHD symptomatology, especially hyperactivity-impulsivity, is related to increased levels of peer victimization. Our model also suggests that larger left CA3 volumes are associated with ADHD symptomatology. In both Clusters 2 and 3, symptoms hyperactivity-impulsivity and inattention are significantly elevated and, in both groups, left CA3 volumes are enlarged compared to Cluster 1, although only significantly enlarged in Cluster 3. Similarities can be seen between our model and the inverse correlation Plessen et al. (2006) observed between CA3 volume and symptoms of inattention in children with ADHD. In our model children in Cluster 3 have the most prominent enlargement of left CA3 volumes, but milder symptoms of inattention than children in Cluster 2. This suggests

the possibility that enlarged left CA3 volumes are representative of a compensatory mechanism by which the hippocampus hypertrophies in response to the presence of ADHD symptoms and results in less severe symptomatology (Plessen et al., 2006). The relationship between symptoms of inattention in children with ADHD and hippocampal volume, specifically in the CA3 subfield should be further explored. Our results suggest that deep phenotyping of brain morphology, cognition, and behaviour can identify subtle differences in ADHD subtypes.

2.4.5 Limitations

A limitation of the current study is our use of a parent-report questionnaire, the CBCL, as a measure of problem behaviour and peer victimization. Children have many experiences without their parents present, such as in school, recreational activities, etc., thus child reports may be able to provide additional information that cannot be captured by parent-report alone. Youth Self Report data was available however not enough children and adolescents completed this questionnaire, which drastically reduced the sample size and power of analyses. Another limitation of the current study was the absence of the ADHD hyperactive/impulsive subtype (ADHD-H). We only had access to data for 15 participants diagnosed with ADHD-H (16.5% of the total ADHD sample), which was not a large enough sample for valid analyses. In children and adolescents ranging from 3 to 18 years of age, ADHD-I is the most common ADHD subtype with a prevalence of between 2.2-5.7%, the prevalence of ADHD-C ranges from 1.1-2.4%, and the prevalence of ADHD-H ranges from 1.1-4.9% (Willcutt, 2012). As children age, an ADHD-H diagnosis becomes less common and could be the reason we had access to the data of very few children with this subtype. Another limitation is that different scanners, with different strengths were used at the various MRI sites. However, a majority of the participants were scanned at CBIC and RU, which both had 3T scanners. The medication status of the children and

adolescents in the study sample are unknown and this is a potential confound for behavioural reports, hippocampal volumes and WM performance.

2.5 Key Points

- Youth with ADHD, particularly those with hyperactivity-impulsivity symptoms, are at an increased risk of experiencing peer victimization.
- Higher levels of peer victimization are associated with increased left CA3 volumes in ADHD-I, ADHD-C, and TD youth.
- Larger left CA3 volumes and smaller left CA4 volumes were associated with better working memory in ADHD-I, ADHD-C and TD youth.

2.6 References

- Achenbach, T. M. (1991). Integrative Guide to the 1991 CBCL/4-18, YSR, and TRF Profiles. Burlington, VT: University of Vermont, Department of Psychology.
- Alexander, L. M., Escalera, J., Ai, L., Andreotti, C., Febre, K., Mangone, A., ... & Litke, S. (2017). An open resource for transdiagnostic research in pediatric mental health and learning disorders. *Scientific Data*, 4, 170181.
- American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5®)*. American Psychiatric Pub.
- Attila, K., Laurel, R., Bender, A. R., Katharina, B., Heim, C., & Lee, S. Y. (2020). Hair cortisol concentrations are associated with hippocampal subregional volumes in children. *Scientific Reports (Nature Publisher Group)*, 10(1).
- Barratt, W. (2006). The Barratt simplified measure of social status (BSMSS). *Indiana State University*.
- Blake, J. J., Kim, E. S., Lund, E. M., Zhou, Q., Kwok, O. M., & Benz, M. R. (2016). Predictors of bully victimization in students with disabilities: A longitudinal examination using a national data set. *Journal of Disability Policy Studies*, 26(4), 199-208.
- Dahmen, B., Puetz, V. B., Scharke, W., von Polier, G. G., Herpertz-Dahlmann, B., & Konrad, K. (2018). Effects of early-life adversity on hippocampal structures and associated HPA axis functions. *Developmental Neuroscience*, 40(1), 13-22.
- Farmer, T. W., Petrin, R. A., Robertson, D. L., Fraser, M. W., Hall, C. M., Day, S. H., & Dadisman, K. (2010). Peer relations of bullies, bully-victims, and victims: The two social worlds of bullying in second-grade classrooms. *The Elementary School Journal*, 110(3), 364-392.

- Frankel, F., & Feinberg, D. (2002). Social problems associated with ADHD vs. ODD in children referred for friendship problems. *Child Psychiatry and Human Development*, *33*(2), 125-146.
- Gadow, K. D., Drabick, D. A., Loney, J., Sprafkin, J., Salisbury, H., Azizian, A., & Schwartz, J. (2004). Comparison of ADHD symptom subtypes as source-specific syndromes. *Journal of Child Psychology and Psychiatry*, *45*(6), 1135-1149.
- Groen, W., Teluij, M., Buitelaar, J., & Tendolkar, I. (2010). Amygdala and hippocampus enlargement during adolescence in autism. *Journal of the American Academy of Child & Adolescent Psychiatry*, *49*(6), 552-560.
- Hanson, J. L., Nacewicz, B. M., Sutterer, M. J., Cayo, A. A., Schaefer, S. M., Rudolph, K. D., ... & Davidson, R. J. (2015). Behavioral problems after early life stress: contributions of the hippocampus and amygdala. *Biological Psychiatry*, *77*(4), 314-323.
- Harms, M. P., Wang, L., Csernansky, J. G., & Barch, D. M. (2013). Structure–function relationship of working memory activity with hippocampal and prefrontal cortex volumes. *Brain Structure and Function*, *218*(1), 173-186.
- Hoogman, M., Bralten, J., Hibar, D. P., Mennes, M., Zwiers, M. P., Schweren, L. S., ... & de Zeeuw, P. (2017). Subcortical brain volume differences in participants with attention deficit hyperactivity disorder in children and adults: a cross-sectional mega-analysis. *The Lancet Psychiatry*, *4*(4), 310-319.
- Humphrey, J. L., Storch, E. A., & Geffken, G. R. (2007). Peer victimization in children with attention-deficit hyperactivity disorder. *Journal of Child Health Care*, *11*(3), 248-260.

- Humphreys, K. L., King, L. S., Sacchet, M. D., Camacho, M. C., Colich, N. L., Ordaz, S. J., ... & Gotlib, I. H. (2019). Evidence for a sensitive period in the effects of early life stress on hippocampal volume. *Developmental Science*, *22*(3), e12775.
- Iglesias, J. E., Augustinack, J. C., Nguyen, K., Player, C. M., Player, A., Wright, M., ... & Alzheimer's Disease Neuroimaging Initiative. (2015). A computational atlas of the hippocampal formation using ex vivo, ultra-high resolution MRI: application to adaptive segmentation of in vivo MRI. *Neuroimage*, *115*, 117-137.
- Janiri, D., Sani, G., De Rossi, P., Piras, F., Banaj, N., Ciullo, V., ... & Spalletta, G. (2019). Hippocampal subfield volumes and childhood trauma in bipolar disorders. *Journal of Affective Disorders*, *253*, 35-43.
- Jonkman, L. M., Markus, C. R., Franklin, M. S., & van Dalen, J. H. (2017). Mind wandering during attention performance: Effects of ADHD-inattention symptomatology, negative mood, ruminative response style and working memory capacity. *PLoS ONE*, *12*(7).
- Kaufman, J., et al. (1997). Schedule for affective disorders and schizophrenia for school-age children-resent and lifetime version (K-SADS-PL): Initial reliability and validity data. *Journal of the American Academy of Child & Adolescent Psychiatry*, *36*(7), 980-988).
- Lee, S. W., Yoo, J. H., Kim, K. W., Kim, D., Park, H., Choi, J., Teicher, M. H., & Jeong, B. (2018). Hippocampal subfields Vol. reduction in high schoolers with previous verbal abuse experiences. *Clinical Psychopharmacology and Neuroscience*, *16*(1), 46–56.
- Liberzon, I., & Abelson, J. L. (2016). Context processing and the neurobiology of post-traumatic stress disorder. *Neuron*, *92*(1), 14-30.
- Martinussen, R., Hayden, J., Hogg-Johnson, S., & Tannock, R. (2005). A meta-analysis of working memory impairments in children with attention-deficit/hyperactivity

- disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, 44(4), 377-384.
- McCloskey, L. A., & Stuewig, J. (2001). The quality of peer relationships among children exposed to family violence. *Development and Psychopathology*, 13(1), 83-96.
- McDaniel, M. A. (2005). Big-brained people are smarter: A meta-analysis of the relationship between in vivo brain volume and intelligence. *Intelligence*, 33(4), 337-346.
- McLaughlin, K. A., Sheridan, M. A., Winter, W., Fox, N. A., Zeanah, C. H., & Nelson, C. A. (2014). Widespread reductions in cortical thickness following severe early-life deprivation: a neurodevelopmental pathway to attention-deficit/hyperactivity disorder. *Biological Psychiatry*, 76(8), 629-638.
- Perlov, E., Philipsen, A., van Elst, L. T., Ebert, D., Henning, J., Maier, S., ... & Hesslinger, B. (2008). Hippocampus and amygdala morphology in adults with attention-deficit hyperactivity disorder. *Journal of Psychiatry & Neuroscience: JPN*, 33(6), 509.
- Plessen, K. J., Bansal, R., Zhu, H., Whiteman, R., Amat, J., Quackenbush, G. A., ... & Hugdahl, K. (2006). Hippocampus and amygdala morphology in attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*, 63(7), 795-807.
- Polanczyk, G., De Lima, M. S., Horta, B. L., Biederman, J., & Rohde, L. A. (2007). The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *American Journal of Psychiatry*, 164(6), 942-948.
- Posner, J., Siciliano, F., Wang, Z., Liu, J., Sonuga-Barke, E., & Greenhill, L. (2014). A multimodal MRI study of the hippocampus in medication-naive children with ADHD: what connects ADHD and depression?. *Psychiatry Research: Neuroimaging*, 224(2), 112-118.

- Quinlan, E. B., Barker, E. D., Luo, Q., Banaschewski, T., Bokde, A. L., Bromberg, U., ... & Garavan, H. (2018). Peer victimization and its impact on adolescent brain development and psychopathology. *Molecular Psychiatry*, 1-11.
- Ramos, A. A., Hamdan, A. C., & Machado, L. (2020). A meta-analysis on verbal working memory in children and adolescents with ADHD. *The Clinical Neuropsychologist*, 34(5), 873-898.
- Riggins, T., Geng, F., Botdorf, M., Canada, K., Cox, L., & Hancock, G. R. (2018). Protracted hippocampal development is associated with age-related improvements in memory during early childhood. *Neuroimage*, 174, 127-137.
- Rogers, M., Hwang, H., Toplak, M., Weiss, M., & Tannock, R. (2011). Inattention, working memory, and academic achievement in adolescents referred for attention deficit/hyperactivity disorder (ADHD). *Child Neuropsychology*, 17(5), 444-458.
- Sapolsky, R. M. (2000). Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. *Archives of General Psychiatry*, 57(10), 925-935.
- Shaw, P., Eckstrand, K., Sharp, W., Blumenthal, J., Lerch, J. P., Greenstein, D. E. E. A., ... & Rapoport, J. L. (2007). Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proceedings of the National Academy of Sciences*, 104(49), 19649-19654.
- Teicher, M. H., Anderson, C. M., Ohashi, K., Khan, A., McGreenery, C. E., Bolger, E. A., ... & Vitaliano, G. D. (2018). Differential effects of childhood neglect and abuse during sensitive exposure periods on male and female hippocampus. *Neuroimage*, 169, 443-452.

- Teicher, M. H., Anderson, C. M., & Polcari, A. (2012). Childhood maltreatment is associated with reduced volume in the hippocampal subfields CA3, dentate gyrus, and subiculum. *Proceedings of the National Academy of Sciences*, *109*(9), E563-E572.
- Tupler, L. A., & De Bellis, M. D. (2006). Segmented hippocampal volume in children and adolescents with posttraumatic stress disorder. *Biological Psychiatry*, *59*(6), 523-529.
- Van Petten, C. (2004). Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: review and meta-analysis. *Neuropsychologia*, *42*(10), 1394-1413.
- Voineskos, A. N., Winterburn, J. L., Felsky, D., Pipitone, J., Rajji, T. K., Mulsant, B. H., & Chakravarty, M. M. (2015). Hippocampal (subfield) volume and shape in relation to cognitive performance across the adult lifespan. *Human Brain Mapping*, *36*(8), 3020-3037.
- Wechsler, D. (2014). *The Wechsler intelligence scale for children—fifth edition*. San Antonio, TX: The Psychological Corporation.
- Willcutt, E. G. (2012). The prevalence of DSM-IV attention-deficit/hyperactivity disorder: a meta-analytic review. *Neurotherapeutics*, *9*(3), 490-499.
- Winters, R. R., Blake, J. J., & Chen, S. (2020). Bully victimization among children with attention-deficit/hyperactivity disorder: a longitudinal examination of behavioral phenotypes. *Journal of Emotional and Behavioral Disorders*, *28*(2), 80-91.
- Wolke, D., Copeland, W. E., Angold, A., & Costello, E. J. (2013). Impact of bullying in childhood on adult health, wealth, crime, and social outcomes. *Psychological Science*, *24*(10), 1958-1970.

Chapter 3

3 Discussion

In this work, we examined whether children with ADHD would exhibit higher levels of social problems compared to TD children. By examining children with different ADHD subtypes, we found differences among the subgroups, TD, ADHD-I and ADHD-C, in severity of problem behaviours and levels of peer victimization. Based on parent report, the ADHD-C group had the most severe aggressive behaviours, rule breaking behaviours, social problems and highest levels of peer victimization when compared to ADHD-I and TD children and youth. The ADHD-I children and youth only differed from the TD group on reported aggressive behaviours, with the ADHD-I group scoring significantly higher. Levels of peer victimization did not differ between the ADHD-I and TD groups. We found left CA3 volume to be a positively associated with peer victimization and WM in all subgroups. Additionally, in all subgroups left CA4 was a negative predictor of WM abilities. Post-hoc cluster analysis suggested that children with ADHD-C with more severe expression of hyperactivity symptoms are the children and youth who are most at risk for experiencing peer victimization.

3.1 Implications

The current study provides insight into the experience of peer victimization, the relationship of peer victimization and brain structure, as well as brain structure and cognitive ability in a large heterogenous sample of children with and without ADHD. Our study highlights the importance of studying peer victimization in all children and youth populations, and specifically the importance of studying its impact on those who are most susceptible. Peer victimization can have serious consequences in childhood and adolescence that can carry forward into adulthood impacting widespread areas of one's life including psychological,

physical, social, and financial wellbeing (Wolke et al., 2013). Our results are in line with previous literature that suggests that those most impacted by peer victimization in the short- and long-term are those that can be described as bully-victims (Winters et al., 2020; Wolke et al., 2013). As peer victimization is a social factor that can be addressed and is a modifiable risk factor for child health, our study highlights the importance of addressing peer victimization with school-based interventions and counselling. While children with ADHD may be more likely to experience peer victimization, all children and youth can benefit from such education and intervention and this might be especially important to those who fall into the bully-victim category (Winters et al., 2020; Wolke et al., 2013).

Our study examined the ADHD population in two subgroups, ADHD-I and ADHD-C, both of adequately large sample size to make valid inferences. Our results highlight the importance of taking into account ADHD subtype and symptomatology severity when studying this population. In study aim 1, we found many significant differences between problem behaviours and significant differences in peer victimization. To reinforce this point, in the cluster analysis, symptomatology severity was a key variable in determining cluster membership. We also found significant differences between the clusters on left CA3 volume, suggesting that symptomatology and severity of symptoms are implicated in brain structure differences and should be considered in future investigation (Al-Amin et al., 2018; Semrud-Clikeman et al., 2017). Further, we found significant differences between the ADHD-I and ADHD-C groups on the WISC-V WMI subscale, with the ADHD-I group displaying significantly poorer performance (Molavi et al., 2020). We also found significant differences between clusters on this measure. This suggests cognitive differences between the subgroups, perhaps also related to symptomatology severity that require further attention and exploration.

Presently, few studies to date have examined the relationship between peer victimization and brain morphology in TD children. Fewer studies have examined these associations in children with ADHD or other neurodevelopmental disorders, despite these children being at greater risk for adverse outcomes. Our study provides valuable insight and demonstrates the importance of studying peer victimization in relation to brain development in child and adolescent populations, especially in ADHD. Further, our study provides support for the notion that the relationship between brain structure and cognitive ability in children and adolescents differs from the relationship observed in adults (Attila et al., 2020; Riggins et al., 2018; Van Petten, 2004).

The similarity of our results to those found in the pediatric PTSD literature, namely the relationship between larger hippocampal volumes and maltreatment, warrants further investigation (Tupler & De Bellis, 2006). Assessing levels of anxiety, fear, and trauma associated with peer victimization might help us better understand how peer victimization affects children and youth with anxiety disorders in addition to ADHD that may identify common underlying mechanisms.

3.2 Future directions

Much of the research including the distinction between ADHD subtypes compare ADHD-I to ADHD-C participants. Inclusion of the ADHD-H subtype and increased data collection from children with this diagnosis can help in making additional inferences about ADHD symptomatology and how it is related to problem behaviours, hippocampal volumes, and cognitive abilities. Thus far, children with ADHD-C have been demonstrated to have the most severe behavioural symptoms compared to the other ADHD subtypes (Gaub & Carlson, 1997). Including ADHD-H children and adolescents in future analyses can help us to get a better

understanding of what has more of an impact on child adolescent functioning, whether it is hyperactivity-impulsivity alone, or whether it is the interaction between hyperactive-impulsive and inattentive symptoms that causes the more severe functional deficits.

The current study focused on peer victimization as a whole, but peer victimization is an umbrella term for different forms of maltreatment, including physical, emotional, and relational abuse (Wiener & Mak, 2009). It would be valuable to assess these different forms of victimization as separate entities in the ADHD population further as it could help determine if types of maltreatment differentially affect children based on their ADHD subtype. Information regarding the forms of peer victimization could inform tailored intervention and counselling strategies in at-risk youths. A future area of study could also examine the different types of bullies and victims (e.g., pure victims, pure bullies, bully-victims, Winters et al., 2020; Wolke et al., 2013) in relation to outcome.

In the current work, parents completed questionnaires regarding social difficulties in relation to their children's in-person social interactions. Of central interest and a future area of study is whether online peer victimization (i.e., Cyberbullying) differs to that experienced at school in children with ADHD. Research indicates that parents are not privy to the cyberbullying that their children might be experiencing or perpetrating (Kowalski & Fedina, 2011). Research also suggests that children with disabilities, including those with ADHD are at an increased risk of experiencing cyberbullying (Kowalski & Fedina, 2011). Dawson et al. (2019) found that adolescents with ADHD reported higher rates of both experiencing and being perpetrators of cyberbullying compared to other adolescents.

Our findings regarding hippocampal volumes indicate a complex relationship with peer victimization, suggesting children with ADHD and TD children may be at comparable risk for

alterations in the development of this key region for learning and memory. We took a region-of-interest approach and chose to study the hippocampus due to its stress sensitive nature; however, the prefrontal cortex is centrally implicated in executive functioning (Friedman & Miyake, 2017) and should be considered in future research in relation to peer victimization, ADHD, and WM.

Parent-report data were used for the problem behaviour and peer victimization measures. Not all data were available for the self-report measures. Examining the differences between youth self-report, parent-report and teacher-report on these various measures would be a good direction for future investigation. It is possible that any one of these measures on their own may not adequately represent the full spectrum of the problem behaviours and victimization that any child or youth might experience.

In this work, we examined data from children and adolescents from age 6 to 18 years, spanning a wide age range. All analyses were adjusted for age. Some studies of maltreatment have provided evidence for a sensitive period in early childhood for the relationship between adversity and hippocampal volume alterations (Humphreys, et al., 2019; Teicher et al., 2018). In the present study, we did not examine the associations within age groups. It would be a worthwhile avenue of future exploration to further investigate the relationship between age and the effects of peer victimization on hippocampal volume as this could further tailor interventions and inform practices of implementation. While recent research has been conducted on the developmental trajectory of children with ADHD in relation to peer victimization status, future research should continue to explore the outcomes of these children and adolescents into adulthood.

3.3 Conclusions

We demonstrated that children diagnosed with ADHD-C seem to differ the most from the TD group on measures of problem behaviour and peer victimization. While the ADHD-I group was statistically similar to the TD group on these measures. We also provided evidence to suggest that peer victimization alters hippocampal structure in both TD and ADHD populations. To our knowledge, this is the first study to examine peer victimization in relation to hippocampal volume in ADHD. We found that the left side of the hippocampus seems to be centrally implicated in changes associated with peer victimization and working memory ability. Additionally, we demonstrated that working memory ability differed between the ADHD-I and ADHD-C subtypes, with ADHD-C being more similar to the TD group than the ADHD-I group on this measure, suggesting differences in cognitive ability between ADHD subtypes. Finally, we found a relationship between hyperactivity and peer victimization risk.

Our study was limited in that parent-report data were used to examine peer victimization and problem behaviour, we were unable to include a sample of ADHD-H participants due to lack of data, different MRI scanning sites used different scanners, and medication usage was unavailable.

Peer victimization is of increasing importance, especially with the rise of technology and the access children and youth have to various social media platforms. This constant access and connectivity to peers can mean it is impossible to escape victimization, even temporarily. The results of this study may inform school psychologists and researchers developing targeted intervention programs for the ADHD population and for other populations disproportionately affected by peer victimization. Future research should focus on examining age with respect to peer

victimization, different types of peer victimization, and should involve further exploration of all the ADHD subtypes.

3.4 References

- Al-Amin, M., Zinchenko, A., & Geyer, T. (2018). Hippocampal subfield volume changes in subtypes of attention deficit hyperactivity disorder. *Brain Research, 1685*, 1-8.
- Attila, K., Laurel, R., Bender, A. R., Katharina, B., Heim, C., & Lee, S. Y. (2020). Hair cortisol concentrations are associated with hippocampal subregional volumes in children. *Scientific Reports (Nature Publisher Group), 10*(1).
- Dawson, A. E., Wymbs, B. T., Evans, S. W., & DuPaul, G. J. (2019). Exploring how adolescents with ADHD use and interact with technology. *Journal of Adolescence, 71*, 119-137.
- Friedman, N. P., & Miyake, A. (2017). Unity and diversity of executive functions: Individual differences as a window on cognitive structure. *Cortex, 86*, 186-204.
- Gaub, M., & Carlson, C. L. (1997). Behavioral characteristics of DSM-IV ADHD subtypes in a school-based population. *Journal of Abnormal Child Psychology, 25*(2), 103-111.
- Humphreys, K. L., King, L. S., Sacchet, M. D., Camacho, M. C., Colich, N. L., Ordaz, S. J., ... & Gotlib, I. H. (2019). Evidence for a sensitive period in the effects of early life stress on hippocampal volume. *Developmental Science, 22*(3), e12775.
- Kowalski, R. M., & Fedina, C. (2011). Cyber Bullying in ADHD and Asperger Syndrome Populations. *Research in Autism Spectrum Disorders, 5*(3), 1201-1208.
- Ladd, G. W., Ettekal, I., & Kochenderfer-Ladd, B. (2017). Peer victimization trajectories from kindergarten through high school: Differential pathways for children's school engagement and achievement?. *Journal of Educational Psychology, 109*(6), 826.
- Molavi, P., Nadermohammadi, M., Ghojehbeiglou, H. S., Vicario, C. M., Nitsche, M. A., & Salehinejad, M. A. (2020). ADHD subtype-specific cognitive correlates and association with self-esteem: a quantitative difference. *BMC Psychiatry, 20*(1), 1-10.

- Riggins, T., Geng, F., Botdorf, M., Canada, K., Cox, L., & Hancock, G. R. (2018). Protracted hippocampal development is associated with age-related improvements in memory during early childhood. *Neuroimage*, *174*, 127-137.
- 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 c controls. *Journal of Attention Disorders*, *21*(12), 1040-1049.
- Teicher, M. H., Anderson, C. M., Ohashi, K., Khan, A., McGreenery, C. E., Bolger, E. A., ... & Vitaliano, G. D. (2018). Differential effects of childhood neglect and abuse during sensitive exposure periods on male and female hippocampus. *Neuroimage*, *169*, 443-452.
- Tupler, L. A., & De Bellis, M. D. (2006). Segmented hippocampal volume in children and adolescents with posttraumatic stress disorder. *Biological Psychiatry*, *59*(6), 523-529.
- Van Petten, C. (2004). Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: review and meta-analysis. *Neuropsychologia*, *42*(10), 1394-1413.
- Wiener, J., & Mak, M. (2009). Peer victimization in children with attention-deficit/hyperactivity disorder. *Psychology in the Schools*, *46*(2), 116-131.
- Winters, R. R., Blake, J. J., & Chen, S. (2020). Bully victimization among children with attention-deficit/hyperactivity disorder: a longitudinal examination of behavioral phenotypes. *Journal of Emotional and Behavioral Disorders*, *28*(2), 80-91.
- Wolke, D., Copeland, W. E., Angold, A., & Costello, E. J. (2013). Impact of bullying in childhood on adult health, wealth, crime, and social outcomes. *Psychological Science*, *24*(10), 1958-1970.

Appendices

Appendix A: Child Mind Institute Biobank Data Transfer Agreement

Template Approved April 2019

CHILD MIND INSTITUTE BIOBANK

RECIPIENT INFORMATION AND CERTIFICATIONS

First Name: Emma Last Name: Duerden
 Degree: PhD Academic Position (or Title): Assistant Professor
 Institution: The University of Western Ontario Department: Faculty of Education
 Street Address: [REDACTED]
 City: [REDACTED] State/Province: [REDACTED]
 Zip/Postal Code: [REDACTED] Country: [REDACTED]
 Telephone: [REDACTED] FAX: [REDACTED]
 E-mail Address: [REDACTED]

Research Project (title): Early adversity and the association with hippocampal development and cognitive ability

Data Requested (check all that apply): HBN

Standard Scope of Work:

"To determine if early adversity predicts altered hippocampal development. The early adversity data will be examined in relation to hippocampal volumes segmented using an automatic segmentation pipeline. Hippocampal volumes will be assessed in relation to cognitive outcome measures. It is predicted that children exposed to early adverse events will have decreased volumes of the hippocampi and adverse cognitive outcomes."

* To request any additions to the Standard Scope of Work, please attach a page(s) to this application with detailed information regarding your request. By signing and dating this DUA as part of requesting access to Biobank Data, Recipient Institution's authorized institutional official and I certify that Recipient will abide by the DUA and the principles, policies and procedures for the use of the Biobank Data. Recipient Principal Investigator further certifies that he/she has shared this document and the relevant Biobank Data policies and procedures with any research staff who will access the Biobank Data. Recipient Institution's authorized institutional official further certifies that he/she has shared this document and the relevant Biobank Data policies and procedures with appropriate institutional entities and individuals.

Recipient Principal Investigator

Signature: [REDACTED]
 Name: Emma Duerden
 Title: Assistant Professor
 Institution: The University of Western Ontario
 Date: 17-May-2019

Recipient Institution (by authorized institutional official)

Signature: [REDACTED] ^{FOR:}
 Name: Dr. Mark Daley
 Title: Associate Vice-President, Research
 Institution: The University of Western Ontario
 Date: May 21, 2019

Appendix B: Child Behaviour Checklist (CBCL)**Questions**

1. Acts too young for his/her age
2. Drinks alcohol without parents' approval
3. Argues a lot
4. Fails to finish things he/she starts
5. There is very little he/she enjoys
6. Bowel movements outside toilet
7. Bragging, boasting
8. Can't concentrate, can't pay attention for long
9. Can't get his/her mind off certain thoughts; obsessions
10. Can't sit still, restless or hyperactive
11. Clings to adults or too dependent
12. Complains of loneliness
13. Confused or seems to be in a fog
14. Cries a lot
15. Cruel to animals
16. Cruelty, bullying, or meanness to others
17. Daydreams or gets lost in his/her thoughts
18. Deliberately harms self or attempts suicide
19. Demands a lot of attention
20. Destroys his/her own things
21. Destroys things belonging to his/her family or others
22. Disobedient at home
23. Disobedient at school
24. Doesn't eat well
25. Doesn't get along well with other kids
26. Doesn't seem to feel guilty after misbehaving
27. Easily jealous
28. Breaks rules at home, school, or elsewhere
29. Fears certain animals, situations, or places, other than school
30. Fears going to school
31. Fears he/she might think or do something bad
32. Feels he/she has to be perfect
33. Feels or complains that no one loves him/her
34. Feels others are out to get him/her
35. Feels worthless or inferior
36. Gets hurt a lot, accident-prone
37. Gets in many fights

38. Gets teased a lot
39. Hangs around with others who get in trouble
40. Hears sounds or voices that aren't there
41. Impulsive or acts without thinking
42. Would rather be alone than with others
43. Lying or cheating
44. Bites fingernails
45. Nervous, high strung, or tense
46. Nervous movements or twitching
47. Nightmares
48. Not liked by other kids
49. Constipated, doesn't move bowels
50. Too fearful or anxious
51. Feels dizzy or lightheaded
52. Feels too guilty
53. Overeating
54. Overtired without good reason
55. Overweight
56. Physical problems without known medical cause
 - 56A. Aches or pains (not stomach or headaches)
 - 56B. Headaches
 - 56C. Nausea, feels sick
 - 56D.A. Problems with eyes (not if corrected by glasses)
 - 56E. Rashes or other skin problems
 - 56F. Stomach aches
 - 56G. Vomiting, throwing up
 - 56H.A. Other
57. Physically attacks people
58. Picks nose, skin, or other parts of body
59. Plays with own sex parts in public
60. Plays with own sex parts too much
61. Poor school work
62. Poorly coordinated or clumsy
63. Prefers being with older kids
64. Prefers being with younger kids
65. Refuses to talk
66. Repeats certain acts over and over; compulsions
67. Runs away from home
68. Screams a lot
69. Secretive, keeps things to self

70. Sees things that aren't there
71. Self-conscious or easily embarrassed
72. Sets fires
73. Sexual problems
74. Showing off or clowning
75. Too shy or timid
76. Sleeps less than most kids
77. Sleeps more than most kids during day and/or night
78. Inattentive or easily distracted
79. Speech problem
80. Stares blankly
81. Steals at home
82. Steals outside the home
83. Stores up too many things he/she doesn't need
84. Strange behavior
85. Strange ideas
86. Stubborn, sullen, or irritable
87. Sudden changes in mood or feelings
88. Sulks a lot
89. Suspicious
90. Swearing or obscene language
91. Talks about killing self
92. Talks or walks in sleep
93. Talks too much
94. Teases a lot
95. Temper tantrums or hot temper
96. Thinks about sex too much
97. Threatens people
98. Thumb-sucking
99. Smokes, chews, or sniffs tobacco
100. Trouble sleeping
101. Truancy, skips school
102. Underactive, slow moving, or lacks energy
103. Unhappy, sad, or depressed
104. Unusually loud
105. Uses drugs for nonmedical purposes (don't include alcohol or tobacco)
106. Vandalism
107. Wets self during the day
108. Wets the bed
109. Whining

110. Wishes to be of opposite sex
 111. Withdrawn, doesn't get involved with others
 112. Worries
 113. Please write in any problems your child has that were not listed above
 113A. Has other problem
 113B. Has other problem
 113C. Has other problem
-

Scores

Anxious/Depressed Raw Score

Withdrawn/Depressed Raw Score (*Sum 8 items: 5, 42, 65, 69, 75, 102, 103, 111*)

Somatic Complaints Raw Score

Social Problems Raw Score (*Sum 11 items: 11, 12, 25, 27, 34, 36, 38, 48, 62, 64, 79*)

Thought Problems Raw Score

Attention Problems Raw Score

Rule Breaking Behavior Raw Score (*Sum 17 items: 2, 26, 28, 39, 43, 63, 67, 72, 73, 81, 82, 90, 96, 99, 101, 105, 106*)

Aggressive Behavior Raw Score (*Sum 18 items: 3, 16, 19, 20, 21, 22, 23, 37, 57, 68, 86, 87, 88, 89, 94, 95, 97, 104*)

Other Problems Raw Score

Internalizing Raw Score

Externalizing Raw Score

Peer Victimization Raw Score (*Sum 4 items: 25, 38, 37, 48*)

Total Raw Score

Each question is scored on a scale from 0-2 according to the value labels listed below:

Value Labels

0=Not true

1=Somewhat or sometimes true

2=Very true or often true

Appendix C: Strengths and Weaknesses Assessment of ADHD and Normal Behaviour (SWAN)

Questions

1. Gives close attention to detail and avoids careless mistakes
2. Sustains attention on tasks or play activities
3. Listens when spoken to directly
4. Follows through on instructions and finishes school work and chores
5. Organizes tasks and activities
6. Engages in tasks that require sustained mental effort
7. Keeps track of things necessary for activities (doesn't lose them)
8. Ignores extraneous stimuli
9. Remembers daily activities
10. Sits still (controls movement of hands or feet or controls squirming)
11. Stays seated (when required by class rules or social conventions)
12. Modulates motor activity (inhibits inappropriate running or climbing)
13. Plays quietly (keeps noise level reasonable)
14. Settles down and rests (controls excessive talking)
15. Modulates verbal activity (controls excessive talking)
16. Reflects on questions (controls blurting out answers)
17. Awaits turn (stands in line and takes turns)
18. Enters into conversation and games without interrupting or intruding

Scoring

Inattention Average

Hyperactivity-Impulsivity Average

SWAN Average

Each question is scored on a scale from -3 to 3 according to the value labels listed below:

Value Labels

-3= Far above average

-2= Above average

-1= Slightly above average

0= Average

1= Slightly below average

2= Below average

3= Far below average

Appendix D: Wechsler Intelligence Scale for Children-V (WISC-V) Working Memory Index**Digit Span**

Experimenter reads a sequence of numbers to the examinee and the examinee is asked to verbally recall the number sequence in either the forward or backwards order.

Forward

Sequences

5, 8, 2

6, 9, 4

Backward

6, 2, 9

4, 1, 5

Picture Span

Experimenter shows a series of pictures to the examinee, then the examinee is given a larger array of pictures and is asked to point to the pictures they previously saw, in the same order they were depicted in.



Curriculum Vitae
Alissa Papadopoulos
 Faculty of Education
 University of Western Ontario

Education

- 2019 – Present Masters of Arts – Counselling Psychology
 University of Western Ontario, London, ON
 Thesis Title: Adversity, Neurodevelopment, and Cognition in Attention Deficit Hyperactivity Disorder.
 Advisor: Dr. Emma G Duerden, PhD.
- 2018 – 2019 Post-Graduate Certificate – Applied Clinical Research
 McMaster University Continuing Education, Hamilton, ON
- 2011 – 2016 Honours Bachelor of Science – Biology and Psychology
 McMaster University, Hamilton, ON
 Thesis Title: Early Autism Study: Tracking ASD Development in Early Childhood.
 Advisor: Dr. M.D. Rutherford, PhD

Research Experience

- 2019 – Present Graduate Student Assistant
 University of Western Ontario, London, ON
 Supervisor: Dr. Emma G. Duerden
- 2016 – 2019 Research Assistant
 Baycrest Health Sciences/Rotman Research Institute, Toronto, ON
 Supervisors: Dr. Brian Levine, PhD and Dr. Gary Naglie, MD
- 2015 – 2016 Research Assistant
 St. Joseph's Healthcare Hamilton, Hamilton, ON
 Supervisor: Dr. Meir Steiner, MD, PhD

Publications

- 2021 **Papadopoulos, A.**, Nichols, E.S., Mohsenzadeh, Y., Giroux, I., Mottola, M.F., Van Lieshout, R.J., Duerden, E.G. (revise and resubmit). Depression in pregnant women with and without COVID-19. *BJpsch Open*.
- 2021 **Papadopoulos, A.**, Seguin, D., Correa, S., Duerden, E.G. (under review). Peer victimization and the association with hippocampal development and working memory in children with and without ADHD. *Scientific Reports*.

- 2020 Renoult, L., Armson, M. J., Diamond, N. B., Fan, C. L., Jeyakumar, N., L., Oliva, L., McKinnon, M., **Papadopoulos, A.**, Selarka, D., St. Jacques, P., & Levine, B. (2020). Classification of general and personal semantic details in the Autobiographical Interview. *Neuropsychologia*, *144*, 107501.

Presentations

- 2021 **Papadopoulos, A.**, Seguin, D., Duerden, E.G. (April 2021). Social Problems and Peer Victimization in Children with ADHD: Examination of Behavioural Phenotypes. Presented at Society for Research in Child Development Virtual Biennial Meeting.
- 2017 Dey, A.K., Stamenova, V., **Papadopoulos, A.**, Oliva, L., Levesque, L., Turner, G., Black, S.E., & Levine, B. (2017). Functional neural correlates of selective attention deficits in Cerebral Small Vessel Disease: a multi-modal approach to exploring variability in vascular cognitive impairment. Presented at the Cognitive Neuroscience Society Conference in San Francisco, USA.
- 2016 **Papadopoulos, A.** & Rutherford, M. (2016). Early Autism Study: Tracking ASD Development in Early Childhood. Presented at the 2016 McMaster Undergraduate Psychology Thesis Conference in Hamilton, Ontario.

Scholarships and Awards

- 2019 – 2021 Graduate Student Assistanship Scholarship
- 2019 Eglinton-Lawrence Volunteer Service Award
- 2011 McMaster University Entrance Scholarship

Workshops and Certificates

- 2018 Applied Suicide Intervention Skills Training (ASIST)
- 2018 CITI Program – Good Clinical Practice (GCP)
- 2017 Mental Health in Geriatrics: Overcoming Suicide and Finding Meaning in Life

2016 Tri-Council Policy Statement: Ethical Conduct for research Involving Humans (TCPS2)

Relevant Professional and Volunteer Experience

2020 – Present Personal Counselling Intern at Fanshawe College

2020 – Present DBT Intern Facilitator at CMHA Elgin Middlesex

2019 – Present Volunteer Crisis Textline Responder

2016 – 2019 Telephone Support Volunteer at Baycrest Seniors Support Program

2013 – 2014 NeuroXchange Undergraduate Research Conference Co-Chair