Behavioural Inhibition as a Risk Factor for Mood and Anxiety Disorders

by

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ABSTRACT

Mood and anxiety disorders are leading causes of disability worldwide. Thus, early intervention strategies are needed. Behavioural inhibition (BI) has been proposed as a risk factor for these disorders, however, the strength and specifity of these associations are unclear. In study 1, using meta-analysis methodology I established the prospective relationship between BI and anxiety disorders. I found BI in childhood was a significant predictor of anxiety at follow-up. In study 2, I investigated BI using an observational assessment in 59 preschool-aged children of parents with mood disorders, anxiety disorders, and controls. I found BI was most strongly associated with parental diagnosis of anxiety disorders, although this relationship did not reach statistical significance. These findings suggest BI is a strong risk factor for anxiety, and may be a marker of familial risk for anxiety disorders. Targeting BI, especially in children of parents with anxiety, may be beneficial for developmental outcomes.

LIST OF ABBREVIATIONS USED

ADHD	Attention-Deficit/Hyperactivity Disorder
BI	Behavioural inhibition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
FORBOW	Families Overcoming Risks and Building Opportunities for Wellbeing
GAD	Generalized Anxiety Disorder
GLLAMM	Generalized Linear Latent and Mixed Models
K-SADS	Kiddie Schedule for Affective Disorders and Schizophrenia
LABTAB	Laboratory Temperament Assessment Battery – Preschool Version
M	Mean
MGH	Massachusetts General Hospital
N	Number
OR	Odds Ratio
SAD	Social Anxiety Disorder
SADS	Schedule for Affective Disorders and Schizophrenia
SD	Standard Deviation
SCID	Structured Clinical Interview for DSM 5 Disorders
95% CI	95% Confidence Interval

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CHAPTER 1 INTRODUCTION

1.1 Mood and Anxiety Disorders

1.1.1 Mood Disorders

Mood disorders, including major depressive disorder and bipolar disorder, are some of the most costly and disabling diseases with onset typically in late adolescence or early adulthood (Uher & Zwicker, 2017). After onset of these disorders early in life they are associated with a number of negative outcomes including unemployment, interpersonal problems, and suicide (Harvey, 2011; Kessler et al., 2005). In addition, after the onset of major depressive disorder or bipolar disorder individuals may never return to their prior level of functioning (Green et al., 2013; Jacob, 2015). Thus early intervention and treatment strategies for individuals at risk for mood disorders may reduce the burden of illness for both affected individuals and society.

1.1.2 Anxiety Disorders

Anxiety disorders are the most common psychiatric disorders and the sixth leading cause of disability worldwide (Bandelow & Michaelis, 2015; Baxter et al., 2014; Kessler et al., 2005). Anxiety disorders are associated with a number of negative outcomes, including increased risk of additional psychiatric disorders such as depression and bipolar disorder, unemployment, social isolation, harmful substance use and suicide (Bandelow & Michaelis, 2015; Kim-Cohen et al., 2003; Nepon et al., 2010). Hence early identification of children at risk for anxiety is essential in order to implement effective preventative strategies.

1.1.3 Comorbidity of Mood and Anxiety Disorders

Mood and anxiety disorders frequently co-occur, and the onset of anxiety disorders increases risk of mood disorder onset, and vice versa (Schaffer et al., 2012;

Woo et al., 2019). It is estimated one-half of people with bipolar disorder (Pavlova et al., 2015), and up to 60% of people with major depressive disorder, also have a comorbid anxiety disorder (Kaufman & Charney, 2000). The presence of both a mood and anxiety disorder is associated with unfavourable outcomes including more frequent episodes of depression and mania, poorer response to medication, lower quality of life, and increased risk of suicide (Goldberg & Fawcett, 2012; Schaffer et al., 2012). The high co-occurrence of mood and anxiety disorders suggests there may be overlap in their etiology. Given the shared vulnerability for mood and anxiety disorders identifying risk factors that are common across these disorder may not only aid in the understanding of disease etiology, but also inform intervention strategies aimed at preventing their onset.

1.2 Offspring of Parents with Mood and Anxiety Disorders

1.2.1 Familial Transmission of Mood and Anxiety Disorders

The strongest known risk factor for major depressive disorder and bipolar disorder is having a parent with a mood disorder. Offspring of parents with major depressive disorder and bipolar disorder are at a two- to five-fold increased risk for a mood disorder by early adulthood compared to control offspring (Rasic et al., 2014). Furthermore, this risk is not disorder specific, with offspring of parents with major depressive disorder at increased risk for both depression and bipolar disorder, and vice versa (Rasic et al., 2014). Offspring of parents with mood disorders are also at increased risk for anxiety diagnoses (Rasic et al., 2014). Compared to controls, offspring of parents with major depressive disorder and bipolar disorder are two times more likely to develop an anxiety disorder by adulthood (Rasic et al., 2014). Prospective familial high-risk studies also suggest that anxiety disorders may precede the onset of mood disorders in high risk

offspring (Sandstrom et al., 2019b). Indeed, a staging model for bipolar disorder in familial high-risk offspring suggests that anxiety disorders may develop as the first manifestation of psychopathology in youth who will go on to develop bipolar disorder (Duffy et al., 2017). This model may also apply to the development of mood disorders in offspring of parents with major depressive disorder (Biederman et al., 2007). Thus, anxiety disorders are also an antecedent of mood disorders.

Similar to mood disorders, one of the strongest risk factors for anxiety disorders is having a parent with an anxiety disorder (Lawrence et al., 2019; Micco et al., 2009). A previous meta-analysis which assessed risk of anxiety disorders in offspring of parents with anxiety found that anxiety diagnoses were almost four times more common in individuals who had a parent with an anxiety disorder compared to controls (Micco et al., 2009). Furthermore, this meta-analysis also established offspring of parents with anxiety are 2.5 times more likely to develop a depressive disorder compared to offspring of control parents (Micco et al., 2009).

1.2.2. Genetic and Environmental Influences

The intergenerational transmission of mood and anxiety disorders from parent to child can be attributed to both genetic and environmental factors. Major depressive disorder, bipolar disorder, and anxiety disorders are heritable (Brainstorm Consortium et al., 2018; Eley, 2001.; Shimada-Sugimoto et al., 2015). Recent investigations suggest this heritable risk is due to many genetic variants that each have a small effect on genetic vulnerability for mood and anxiety disorders (Levey et al., 2020; Meier et al., 2019; Uher & Zwicker, 2017). The transmission of these variants is not disorder specific as there is considerable overlap in genetic variants across different mental disorders (Brainstorm

Consortium et al., 2018; Taylor et al., 2018). For example, approximately two-thirds of genetic factors are shared across bipolar disorder and major depressive disorder (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). In addition, it is estimated that 66% of total genetic variance is shared between anxiety and depressive symptoms (Taporoski et al., 2015). Taken together, these findings suggest the intergenerational transmission of anxiety and mood disorders is partly due to genetic factors which may be shared across these disorders.

Environmental factors may also contribute to vulnerability for mood and anxiety disorders in offspring of parents with major depressive disorder, bipolar disorder and anxiety disorders. For example, parent and family stressors are more common in offspring of parents with mood and anxiety disorders, and may increase risk for the onset of these disorders (Beardslee et al., 1998; Ferreira et al., 2013; Platt et al., 2016). In addition, parenting style may also influence vulnerability for mood and anxiety disorders in familial high-risk offspring (Budinger et al., 2013; Kemner et al., 2015; McLeod et al., 2007; Möller et al., 2016; Ryan & Ollendick, 2018). For example, positive parenting styles such as warmth, and encouragement have been found to be protective for the development of mental illness (Budinger et al., 2013; Möller et al., 2016), whereas, negative parenting styles including criticism and rejection may increase risk for later mood and anxiety disorders (Budinger et al., 2013; Kemner et al., 2015; Ryan & Ollendick, 2018). Furthermore, overprotective parenting, defined as excessive comforting when the child exhibits fear and behaviors that shelter children from stress (Clarke et al., 2013; Hutt et al., 2013), has been found to be associated with both depression and anxiety (Hudson & Dodd, 2012; Oldehinkel et al., 2006), and is more common in parents with

mood and anxiety disorders (Clarke et al., 2013; Gomes et al., 2015). Thus, both genetic and environmental factors associated with family history of mood and anxiety disorders contribute to offspring's disease risk.

1.2.3 Antecedents in Offspring of Parents with Mood and Anxiety Disorders

Offspring of parents with mood and anxiety disorders are at increased risk for depression, anxiety, and bipolar disorder. Therefore, studies of these children provide an opportunity to investigate the antecedents of major depressive disorder, bipolar disorder and anxiety disorders, in youth known to be at risk for mood and anxiety disorders (Sandstrom et al., 2019b). Even before the onset of major depressive disorder, bipolar disorder or an anxiety disorder, offspring of parents with mood and anxiety disorders are at an increased risk for the precursors of these disorders (Hafeman et al., 2016; Rice et al., 2017; Sandstrom et al., 2019b; Silverman et al., 1988). Mood and anxiety disorders are highly comorbid and have common genetic and environmental influences. Thus, some risk factors may be shared across offspring of parents with major depressive disorder, bipolar disorder, and anxiety disorders, whereas other risk factors may be specifically associated with one type of parental mental illness (Sandstrom et al. 2019b).

Studies in offspring of parents with mood and anxiety disorders typically focus on risk factors in later childhood and adolescence. However the earliest manifestations of risk for mood and anxiety disorders may be evident prior to this time. Identifying these early risk indicators in the context of positive family history of mood and anxiety disorders may allow for proactive monitoring and preventative strategies at the earliest identifiable stage of risk. Thus, greater focus on risk factors in high-risk offspring in toddlerhood, and early childhood is warranted.

1.3 Behavioural Inhibition

Temperament refers to individual differences in behavioural style, emotional reactivity and regulation, and can be assessed as early as the first few years of life (Saudino, 2005). Temperament contributes to behavioural and emotional variance observed between children, and has a strong influence on later personality (Goldsmith et al., 1987). Temperament is influenced by both genetic and environmental factors. The estimated heritability of temperament based on twin and adoption studies ranges from 20% to 60% depending on the sample (Saudino, 2005). Environmental influences which contribute to the other 40% to 80% of variance have been postulated to include positive behaviors and emotions (e.g. smiling) exhibited by caregivers during infancy, maternal personality, attachment style, and parenting style (Saudino, 2005). Temperament assessed in early childhood has been found to predict the development of psychiatric disorders later in life (Caspi et al., 1996; Grant et al., 2009). One commonly measured temperament dimensions which has been implicated in studies of psychopathology is behavioural inhibition (Clauss & Blackford, 2012; Hirshfeld-Becker et al., 2006).

1.3.1 Etiology

Behavioural inhibition is characterized by shyness, fear and avoidance of novel stimuli (Kagan et al., 1988). Inhibited children exhibit distress in novel situations, limited social behaviors and shyness, and may approach new stimuli with extreme hesitancy (Hirshfeld-Becker et al., 2008; Kagan et al., 1988). A previous investigation found that inhibited preschoolers displayed more reticent and anxious behaviors during free play, and engaged in fewer structured social activities outside of school (Coplan et al., 2009).

Neuroimaging and genetic studies have implicated brain regions and genes which may form the neural and genetic basis of behavioural inhibition. Kagan first proposed children with behavioural inhibition display higher reactivity in the limbic brain regions, and higher heart rate during exposure to the unfamiliar (Kagan et al., 1988). More recent investigations have linked behavioural inhibition with alterations in the brain regions involved in novelty detection, emotion regulation, and attention (Clauss et al., 2015). Findings suggest that inhibited temperament is associated with hyperactivity in the amygdala, hippocampus, basal ganglia, and cerebellum, and decreased prefrontal cortex regulatory control over the amygdala (Clauss et al., 2015). Previous genetic investigations have explored the association between inhibition and candidate genes. The serotonin transporter linked polymorphic region (5-HTTLPR) has frequently been implicated in studies of psychopathology (Margoob & Mushtaq, 2011). The majority of studies on the association between 5-HTTLPR and inhibited temperament have found an association between the short allele and inhibition (Battaglia et al., 2005; Davies et al., 2013; Hayden et al., 2007). However, some previous investigation have found no association between 5-HTTLPR and inhibition (Schmidt et al., 2002), or have found an association between the long allele and shyness (Arbelle et al., 2003; Jorm et al., 2000). Conflicting findings are likely due to the effect of environmental factors on the relationship between the 5-HTTLPR and inhibited temperament. Previous findings indicate that the risk for emotional problems associated with the short allele of the 5-HTTLPR is strongest for children also exposed to adverse environmental influences, including trauma, poor parenting, and low social support (Clauss et al., 2015; Fox et al., 2005). Thus, the 5-HTTLPR may be associated with inhibition, and its influence may be

particularly strong when children are also exposed to these environmental factors (Clauss et al., 2015). The corticotropin releasing hormone gene (CRH), and the corticotropin releasing hormone receptor 1 gene (CRHR1) involved in the hypothalamic-pituitary adrenal axis which regulates the body's stress response, have both been found to be associated with inhibited temperament (Rogers et al., 2013; Smoller et al., 2003, 2005). Taken together, findings from neuroimaging and genetic studies suggest that brain regions involved in the fear response, the 5-HTTLPR, and genes linked with the body's stress response may contribute to the biological basis of inhibited temperament.

1.3.2 Behavioural Inhibition and Psychiatric Disorders

Previous investigation have implicated behavioral inhibition as a risk factor for mood and anxiety disorders (Caspi et al., 1996; Hudson et al., 2018). Behavioral inhibition and related constructs have also been described in association with other psychiatric disorders including autism (Clifford et al., 2013) and reactive attachment disorder (Zeanah & Fox, 2004). However, for the purpose of this thesis the following paragraphs focus solely on past investigations which have assessed the relationship between behavioural inhibition and major depressive disorder, bipolar disorder, and/or anxiety disorders.

Behavioural inhibition is one of strongest predictors of subsequent anxiety disorders (Hirshfeld-Becker et al., 2008; Hudson et al., 2018; Rapee et al., 2009). Previous investigations have established that behavioural inhibition in early childhood increases risk of anxiety in later childhood, adolescence and adulthood (Frenkel et al., 2015; Hudson et al., 2011, 2018; Hudson & Dodd, 2012; Schwartz et al., 1999). While the relationship between behavioural inhibition and anxiety is well established, the

strength of this relationship varies between studies, with effect sizes ranging from small (Hirshfeld-Becker et al., 2007) to large (Essex et al., 2010; Hudson et al., 2011; Muris et al., 2011). In addition, there is evidence that behavioural inhibition may be a risk factor specific to social anxiety disorder. Indeed a previous meta-analysis established behavioural inhibition was associated with a more than sevenfold increase in odds of social anxiety disorder by follow-up compared to uninhibited children (Clauss & Blackford, 2012). Findings regarding an association between behavioural inhibition and other types of anxiety disorders are mixed, with some studies finding an association (Hudson et al., 2011; Moffitt et al., 2007) and others finding no association (Biederman et al., 1993; Hirshfeld-Beckeret al., 2007). Thus, clarification of the relationship between behavioural inhibition and anxiety disorders is needed.

Previous research suggests that behavioural inhibition may also be associated with depression. One investigation of children aged 5-8 found that behavioural inhibition was prospectively associated with depressive symptoms one year later (Muris et al., 2011). In addition, a study based on retrospective assessment of inhibited temperament found that participants with a depressive disorder reported higher childhood behavioural inhibition (Gladstone & Parker, 2006). The Dunedin study assessed children's temperament at age three using an observational assessment. Children classified as inhibited were found to be more likely to meet diagnostic criteria for depression by age 21 (Caspi et al., 1996). Taken together, these findings provide preliminary evidence for an association between behavioural inhibition and depression. However, future research is needed to confirm these findings. To my knowledge, there are no prospective studies that have assessed the

relationship between behavioural inhibition in early childhood and the onset of bipolar disorder later in life.

There is a gap in the literature on the prospective association between behavioural inhibition and subsequent mood disorders. Longitudinal research is needed to determine the predictive validity of behavioural inhibition for major depressive disorder, and bipolar disorder. However, longitudinal research takes many years to complete. In the meantime, utilizing the familial high-risk approach provides the opportunity to study behavioural inhibition as a risk factor for major depressive disorder and bipolar disorder in individuals known to be at-risk for mood disorders. This may provide preliminary findings regarding the associations between behavioural inhibition and mood disorders, which may inform future research and early intervention strategies. In addition, the inclusion of offspring of parents with anxiety disorders alongside offspring of parents with mood disorders will allow for the comparison of behavioural inhibition across different familial high-risk groups.

1.4 Behavioural Inhibition in Offspring of Parents with Mood and Anxiety Disorders

Previous research in offspring of parents with anxiety disorders suggests behavioural inhibition may be linked with parental anxiety. For example, one investigation found that toddlers of parents with social anxiety disorder showed more fear and avoidance during a novel social referencing situation than children of parents with other anxiety disorders, and control children (Aktar et al., 2014). Another study found that infants of mothers with an anxiety disorder showed more distress when faced with novelty than infants of mothers without an anxiety disorder (Reck et al., 2013). Parental

depression has also been linked with behavioural inhibition. For instance, one study found that children with higher levels of behavioural inhibition had a higher probability of having a depressed parent (Olino et al., 2010). To my knowledge, there are no studies that have exclusively assessed the relationship between behavioural inhibition and family history of bipolar disorder in preschool aged offspring. However, a study of adolescent offspring of parents with bipolar disorder which used a self-report of inhibition found that offspring of parents with bipolar disorder who had mood symptoms themselves had higher inhibited temperament compared to the control group (Kim et al., 2017). On the other hand, asymptomatic (i.e., no mood symptoms) offspring of parents with bipolar disorder were found to have lower inhibited temperament compared to the control group (Kim et al., 2017). While these findings are somewhat counter-intuitive it should be noted that sample size of the three groups was small. Furthermore the reliance on self-report of inhibition may have been influenced by desirability bias leading to inaccurate estimates of temperament (Huang et al., 1998).

There are a limited number of studies that have compared behavioural inhibition in offspring across different parental diagnoses. One previous investigation compared behavioural inhibition in offspring of mothers with unipolar depression, bipolar disorder, and no history of mental illness. Behavioural inhibition was found to be significantly higher in offspring of mothers with unipolar depression compared to offspring of mothers with bipolar disorder, and offspring of mothers with no history of mental illness. Behavioural inhibition in offspring of mothers with bipolar disorder was not significantly different from the control group (Kochanska, 1991).

Only two studies (Rosenbaum et al., 2000; Rosenbaum et al., 1988); both from the same study group (Massachusetts General Hospital [MGH]) using different samples, have compared behavioural inhibition across offspring of parents with mood and anxiety disorders. Both studies included children between the ages of 2 and 6 who had a parent that was being treated for panic disorder/agoraphobia, depression, or had no history of mood and anxiety disorders (comparison group). The first study in 1988 found that behavioural inhibition was significantly higher in offspring of parents with panic disorder/agoraphobia with and without comorbid depression compared to the control group (Rosenbaum et al., 1988). Behavioural inhibition was also numerically elevated in offspring of parents with major depressive disorder, however this difference did not reach statistical significance (Rosenbaum et al., 1988). The second study (Rosenbaum et al., 2000) found that compared to the control group behavioural inhibition was significantly higher in offspring of parents with depression with and without comorbid panic disorder/agoraphobia. Behavioural inhibition in offspring of parents with panic disorder/agoraphobia was numerically elevated compared to controls, with a similar effect size to that of offspring of parents with major depressive disorder. However, the difference between offspring of parents with panic disorder/agoraphobia and offspring of control parents did not reach statistical significance, likely due to limited power as the sample size of each group was small. Interestingly, in both studies (Rosenbaum et al., 2000; Rosenbaum et al., 1988) rates of behavioural inhibition were highest in offspring of parents with both panic disorder/agoraphobia and depression. These results suggest that the presence of both disorders in parents may interact to further heighten vulnerability to behavioural inhibition compared to children of parents with only one of these disorders.

In a secondary data analysis of the sample from the second study (Rosenbaum et al., 2000) the authors retrospectively identified parents from the sample who met criteria for bipolar disorder based on previous history of manic or hypomanic episodes reported during a clinical interview (Hirshfeld-Becker et al., 2006). Behavioural inhibition did not differ between offspring of parents with and without bipolar disorder. However, the group of parents without bipolar disorder was composed of parents with panic disorder/agoraphobia, major depressive disorder with and without comorbid panic disorder/agoraphobia, and parents with no history of mood and anxiety disorders. Thus, the inclusion of parents with depression and anxiety may have increased the rates of behavioural inhibition in the comparison group. Indeed, when behavioural inhibition in offspring of parents with bipolar disorder was compared to offspring of parents with unipolar depression, no significant difference was found. Inhibition in this sample was previously found to be elevated in offspring of parents with depression relative to the control group (Rosenbaum et al., 2000). Thus, it is possible that behavioural inhibition may also be elevated in offspring of parents with bipolar disorder compared to offspring of parents with no history of mood and anxiety disorders. In addition, the effect of parents' comorbid anxiety on the association between behavioural inhibition in offspring and family history of bipolar disorder was not explored.

Findings from the MGH study group (Hirshfeld-Becker et al., 2006; Rosenbaum et al., 2000; Rosenbaum et al., 1988) suggest that behavioural inhibition may be an early manifestation of risk for mood and anxiety disorders. However, these findings warrant further clarification. Specially, the sample of parents with depression (Rosenbaum et al., 2000; Rosenbaum et al., 1988) also included a number of parents with bipolar disorder.

Thus, we are unable to determine whether behavioural inhibition is associated with family history of mood disorders in general, or is more closely linked to family history of depression or family history of bipolar disorder. Carefully selecting two distinct groups of parents with either major depression or bipolar disorder is needed. In addition, while the presence of both mood and anxiety disorders in parents is associated with the highest rates of inhibited children, it is not yet clear which of these types of disorders is the stronger predictor of behavioural inhibition. Future research is needed to better elucidate the strength and specificity of the associations between behavioural inhibition and family history of mood and anxiety disorders. This may inform our understanding of the etiology of mood and anxiety disorders, and may assist with the design and implementation of effective early interventions.

1.5 Measurement of Temperament

Parent report questionnaires, and observational measures are the two most common methods used to assess children's temperament, with parent report being the most widely used. Parent reports are the most common measure as they are quick to administer, cost-effective, and provide a rating of the child's behavior across many settings, situations, and time points. However, the use of parent reports poses challenges as parents may not have an accurate representation of their child's behavior (Durbin & Wilson, 2012; Seifer et al., 2004). In addition, as parent questionnaires include some degree of subjective data, reports may be difficult to compare across different children (Mangelsdorf et al., 2000). Finally, reports in parents with mood and anxiety disorders may be influenced by the parent's own mental state and their past experience with mental illness (Maoz et al., 2014; Najman et al., 2000; Sandstrom et al., 2019a).

There are two theories which have been proposed to explain how parents' mental illness may impact the perception of their children's behavior: the distortion model and the accuracy model (Fergusson et al., 1993; Richters, 1992). While both theories were initially proposed with a focus on the role of parents' depressive symptoms on their reports of children's behavior, some previous investigations have suggested these theories also extend to other forms of parent psychopathology (Clark et al., 2017). The distortion model posits that psychiatric symptoms bias parents' perceptions of children's maladaptive behaviors such that these behaviors are over-reported (Fergusson et al., 1993; Richters, 1992). On the other hand, the accuracy model suggests that parents with mental illness report more accurately on children's behavior as the presence of psychiatric symptoms reduces the positive bias often associated with parent report (Seifer et al., 2004). The majority of evidence tends to support the distortion model (Najman et al., 2000; Youngstrom et al., 2001). Therefore, in studies of offspring of parents with mood and anxiety disorder, parents' report of temperament may be biased due to parents over-reporting children's problem behaviors.

Given the drawbacks associated with parent report measures, observational assessments may have the advantage of providing an unbiased estimate of children's temperament. Furthermore, observational measures of temperament have been found to have strong predictive validity for developmental outcomes, and the onset of psychiatric disorders (Dougherty et al., 2013; Durbin et al., 2007; Hayden et al., 2006). Laboratory assessments are sometimes criticized as they only capture children's behavior in one setting, and thus may provide an incomplete representation of children's temperament. However, a previous investigation (Lo et al., 2014) found that children's behavior

exhibited during an observational assessment was rated by parents as highly typical of children's temperament in natural environments.

1.6 Objectives

Further research on behavioural inhibition as a risk factor for mood and anxiety disorders is needed. My thesis attempts to address this gap in the literature by investigating behavioural inhibition as a prospective risk factor for anxiety, and as a potential marker of familial risk for mood and anxiety disorders. In Study 1, I conducted a meta-analysis to quantify the strength of the prospective association between BI and any anxiety, and between BI and specific anxiety disorders. I hypothesized that BI would be a significant predictor of anxiety, and that this relationship would hold for each individual anxiety disorder. In Study 2, I examined behavioural inhibition in offspring of parents with anxiety disorders, major depressive disorder, bipolar disorder, and no history of mental illness (i.e., mood, anxiety, and psychotic disorders). Based on the literature reviewed I predicted behavioural inhibition would be significantly higher in offspring of parents with anxiety disorders, major depressive disorder, and bipolar disorder compared to offspring of parents with no history of mental illness. Furthermore, I hypothesized that the association between behavioural inhibition and family history of mood disorders would be reduced after accounting for parental anxiety. Thus, family history of anxiety disorders would be a stronger predictor for behavioural inhibition than family history of mood disorders.

CHAPTER 2 PROSPECTIVE ASSOCIATION BETWEEN CHILDHOOD BEHAVIOURAL INHIBITION AND ANXIETY: A META-ANALYSIS

Contribution Statement

I conducted the literature search, drafted the manuscript, completed the data analysis, and devised the original idea for the chapter. I received guidance and editing from Dr. Barbara Pavlova, and Dr. Rudolf Uher.

2.1 Abstract

Background: Behavioural inhibition (BI) is a risk factor for anxiety. However, the estimates of the strength of this association vary widely. In addition, while BI is a strong predictor of social anxiety disorder (SAD), its association with other anxiety disorders is unclear. The current study sought to establish the relationship between BI and anxiety and to quantify this association for a range of anxiety disorders.

Methods: We searched PsycInfo, PubMed and Embase for articles published before May 18th, 2019 using search terms for BI, anxiety and prospective study design. We selected articles which assessed the prospective relationship between BI in childhood and anxiety. Using random-effect meta-analysis with robust variance estimation, which allowed for the inclusion of multiple follow-ups of the same sample, we established the association between BI and any anxiety. We also explored the association between BI and individual anxiety disorders.

Results: Data from 27 studies consisting of 35 follow-ups of 20 unique samples indicated that BI prospectively increases the odds of anxiety (OR= 2.80, 95% CI 2.03 to 3.86, $p<0.001$). There was also a positive association between BI and all individual anxiety disorders, with effect sizes ranging from small in the case of specific phobia (OR= 1.49, 95% CI 1.03 to 2.14, $p=0.03$) to large in the case of SAD (OR= 5.84, 95% CI 3.38 to 10.09, $p<0.001$).

Conclusions: BI in early childhood is a strong risk factor for anxiety. Targeting BI may help reduce the number of children who will develop anxiety disorders.

2.2 Introduction

Anxiety disorders are the most common psychiatric disorders and the sixth leading cause of disability worldwide (Bandelow & Michaelis, 2015; Baxter et al., 2014; Kessler et al., 2005). Anxiety disorders that develop in childhood are associated with a number of negative outcomes later in life, including not only anxiety, but also depression, bipolar disorder, unemployment, social isolation, harmful substance use and suicide (Bandelow & Michaelis, 2015; Kim-Cohen et al., 2003; Nepon et al., 2010). Hence early identification of children at risk is essential in order to implement effective preventative strategies.

One of the strongest predictors of anxiety disorders is behavioural inhibition (BI) (Rapee et al., 2009). BI is a temperament style that is characterized by shyness, fear, and avoidance of novel stimuli and situations (Kagan et al., 1999). BI can be indexed as early as the first few years of life (Rapee et al., 2009). While previous investigations generally agree that BI is associated with later anxiety, the estimates of strength of this association vary widely, with the reported odds ratio of anxiety in inhibited children compared to uninhibited children ranging from just over one (Hirshfeld-Becker et al., 2007) to almost ten (Essex et al., 2010; Hudson et al., 2011). A previous meta-analysis established a strong relationship between BI and social anxiety disorder (SAD) (Clauss & Blackford, 2012). However, to our knowledge, there has been no meta-analysis of the association between BI and all anxiety subtypes.

Some previous investigations suggest that BI may be an antecedent specific to SAD (Essex et al., 2010; Hirshfeld-Beckeret al., 2007). Indeed, according to a previous meta-analysis BI is associated with a seven-fold increase in odds of developing SAD

Clauss & Blackford, 2012). The association between BI and other types of anxiety disorders is less clear. For example, while some studies have found that BI is associated with an increased risk for generalized anxiety disorder (GAD) (Hudson et al., 2011; Moffitt et al., 2007), specific phobia (Hudson et al., 2011), and separation anxiety disorder (Biederman et al., 1993), other studies suggest that the number of inhibited children who will develop these anxiety disorders is comparable to that of uninhibited children (Biederman et al., 1993; Hirshfeld-Becker et al., 2007; Hudson et al., 2018; Rapee, 2014).We sought to resolve this inconsistency by quantifying the association between BI and different types of anxiety disorders.

In summary, the aim of this meta-analysis is to quantify the strength of the prospective association between BI and any anxiety, and between BI and specific anxiety disorders.

2.3 Methods

2.3.1 Method Strategy and Selection Criteria

We searched PsycInfo, PubMed and Embase using the combination of search terms for behavioural inhibition ("behavioural inhibition", "inhibited temperament", or "fearful temperament"), prospective study design ("longitudinal" or "prospective" or "follow up") and anxiety ("anxiety disorder" or "anxiety" or "anxiety diagnosis" or "social anxiety disorder" or "generalized anxiety disorder" or "separation anxiety disorder" or "obsessive-compulsive disorder" or "specific phobia" or "social phobia" or "agoraphobia" or "post-traumatic stress disorder"), for articles published up until May 18th, 2019. We searched the reference list of all identified eligible articles and of a recent review (Clauss & Blackford, 2012). We also evaluated all articles which cited an included study or the recent review.

We included studies that reported original data on the prospective relationship between BI and anxiety. Studies were eligible for inclusion if they were longitudinal; first assessing BI and then assessing anxiety at least six months later. Studies which referred to a construct other than BI (i.e., fearful temperament, shyness/inhibition) were also included as long as the definition and measurement of this construct was the same or very similar to that of BI; which was defined as shyness, fear, and avoidance when faced with new stimuli. For the meta-analysis of the relationship between BI and all anxiety subtypes, we included studies that assessed anxiety disorders as well as studies that assessed anxiety symptoms. We excluded studies which did not measure BI in toddlerhood or early childhood (between the ages of 1 and 8) or studies which selected participants based on an anxiety diagnosis at baseline. We excluded overlapping data

from studies which used the same sample unless the publication reported data from a different follow-up period. We did not exclude publications that were not in English, but no publications in any other languages met inclusion criteria. We conducted the meta-analyses of the association between BI and different types of anxiety disorders, if the specific anxiety disorder was assessed in at least five studies (Jackson & Turner, 2017).

We contacted the corresponding authors of included studies to request additional data and when it was unclear whether the study met the inclusion criteria. However, we did not receive a response in every case.

2.3.2 Data Extraction

Citations from the systematic search were imported into Covidence (systematic review platform). Screening was completed by the first author and the full text review to determine study eligibility was completed by two authors (AS and BP). Discrepancies between the two authors were resolved in consensus meetings.

The following information was extracted from the eligible articles: author, study year, country, number of males and females, ethnicity of participants (percentage Caucasian), age of participants at BI assessment (*M*, *SD* and age range), age of participants at anxiety assessment (*M*, *SD* and age range), the time delay between the BI and anxiety assessments, the tool used to measure BI (questionnaire or observation), the tool used to assess anxiety (interview or questionnaire), the types of anxiety measured (symptoms or disorders), comparability of groups (whether groups were representative of the population or selected based on extreme ends of the inhibited spectrum), and study quality. Study quality was assessed using adapted criteria from the Standard Quality Assessment Criteria for Evaluating Primary Research Papers for Quantitative Studies

(Kmet et al., 2004). We evaluated quality of individual studies based on the quality of the measure of BI, the quality of the measure of anxiety, and the characteristics/selection of participants (see table 2.2 in the supplement for full details).

When possible we also extracted data for prevalence of individual anxiety disorders separately (SAD, GAD, separation anxiety, specific phobia, panic disorder, agoraphobia, obsessive compulsive disorder [OCD], post-traumatic stress disorder [PTSD]). When BI was assessed multiple times, we followed the BI designation (inhibited or not) defined by the study authors. In one study (Prior et al., 2000) no designation was provided. In this case, we classified children as inhibited if they were rated as "shy" on at least six out of eight assessment. We chose this classification as it most closely resembled that used in other studies, which classified children as inhibited if they demonstrated high BI across the majority of temperament assessments. In studies which provided data separately for individuals with and without BI we extracted the number of participants in each group at baseline who also returned for the follow-up assessment and the number of individuals in each group at follow-up who developed an anxiety diagnosis. In studies that provided a correlation between BI and anxiety we extracted the correlation. One study (Biederman et al., 1993) used the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III) (American Psychiatric Association, 1980) to diagnose childhood anxiety disorders which included overanxious disorder and avoidant disorder. As in subsequent DSM editions overanxious disorder is encompassed in GAD diagnosis and avoidant disorder is recognized to exist on the social phobia spectrum (American Psychiatric Association, 1987), children who received a

diagnosis of overanxious or avoidant disorder were included in our GAD or SAD analysis respectively.

2.3.3 Statistical Analysis

We performed all data analyses using Stata 15 (StataCorp, 2017). We converted extracted data to odds ratio (OR) effect sizes using an online calculator (Wilson, 2000) accessed through the Campbell Collaboration; a methodological support service for systematic reviews. When studies reported the correlation between BI and anxiety we converted it to the natural ln (OR) using a validated equation outlined by the Campbell Collaboration (Polanin & Snilstveit, 2016). Odds ratios (ORs) reflected the probability of anxiety by follow-up. ORs greater than 1 represent an increased likelihood of anxiety in individuals who had BI at baseline compared to individuals who did not have BI at baseline.

We first performed a meta-analysis of the risk for any type of anxiety using a random-effect model meta-analysis with robust variance estimation to account for the non-independence of multiple effect sizes from the same sample, implemented through the *robumeta* program (Tanner-Smith & Tipton, 2014). This allowed for the inclusion of multiple follow-ups of the same group of participants.

We then ran four more random effects model meta-analyses looking at the relationship between BI, and GAD, SAD, specific phobia, and separation anxiety disorder. As there were less than five studies which assessed panic disorder, agoraphobia, PTSD and OCD, we were not able to assess the association between BI and any of these anxiety disorders. We reported pooled effect sizes as ORs with their 95% confidence intervals and p values. We considered p-values smaller than 0.05 statistically significant.

We also tested heterogeneity between studies using the I^2 statistic and tau^2 statistic. We explored the effect of study characteristics (sex[percentage of males], age at BI assessment, BI measure [observational, parent-report or both], anxiety measure [interview or questionnaire], age at anxiety assessment, geographic region, year of publication, whether BI was assessed more than once, time between BI and anxiety assessments, comparison of groups [general population or extreme ends of inhibited spectrum], and study quality) on the association between BI and subsequent anxiety using meta-regressions. We report the results of the meta-regressions as the standardized regression coefficients (*beta*), their 95% confidence intervals and p-values.

We assessed publication bias through visual inspection of funnel plots, and the Egger's Intercept test. However, as these tests require statistical independence and have not been validated for meta-analyses using robust variance estimation, we aggregated effect sizes across overlapping samples. Thus, our assessment of publication bias was based on one estimate per sample.

Finally, we performed a sensitivity analysis to further explore the effect of study quality by restricting our analysis to studies of higher quality (quality scored 3 out of 5 or higher).

2.4 Results

Out of 880 studies identified in our literature search, we excluded 823 articles after abstract screening. The full-text review of the remaining 57 articles identified 27 eligible studies comprised of 35 follow-ups and 20 non-overlapping samples (**Figure 2.1**), with a total of 8836 children (48.5% male). 10 studies consisting of a total of 1573 participants assessed the association between BI and SAD. Eight studies composed of

1589 participants quantified the association between BI and GAD. Seven studies of 1022 participants assessed the relationship between BI and specific phobia. Finally, six studies with 962 participants assessed the relationship between BI and separation anxiety disorder. The mean age at the BI assessment was 3.67 years (SD= 1.69, range = 1.05 to 9.5) and the mean age at the anxiety assessment was 10.39 years (SD= 6.00, range = 2.55 to 32) with an average 6.83 years (SD= 5.89, range = 1 to 28) in between these two assessments.

BI significantly increased the subsequent risk of anxiety (OR= 2.80, 95% CI 2.03 to 3.86, p<0.001; **Figure 2.2**). We noted moderate heterogeneity between studies (tau^2 = 0.07, I^2=38.03%). Children with BI were significantly more likely to have SAD (OR= 5.84, 95% CI 3.38 to 10.09, p<0.001; **Figure 2.3**), GAD (OR= 2.04, 95% CI 1.43 to 2.91, p<0.001; **Figure 2.4**), and specific phobia (OR= 1.49, 95% CI 1.03 to 2.14, p=0.03; **Figure 2.5**) at follow-up compared to children without BI. Despite a similar effect size, BI did not significantly predict separation anxiety at follow-up (OR= 1.84, 95% CI 0.88 to 3.85, p=0.11; **Figure 2.6**).

Figure 2.1. Prisma Flow Diagram (Moher et al., 2009) of literature search and study eligibility

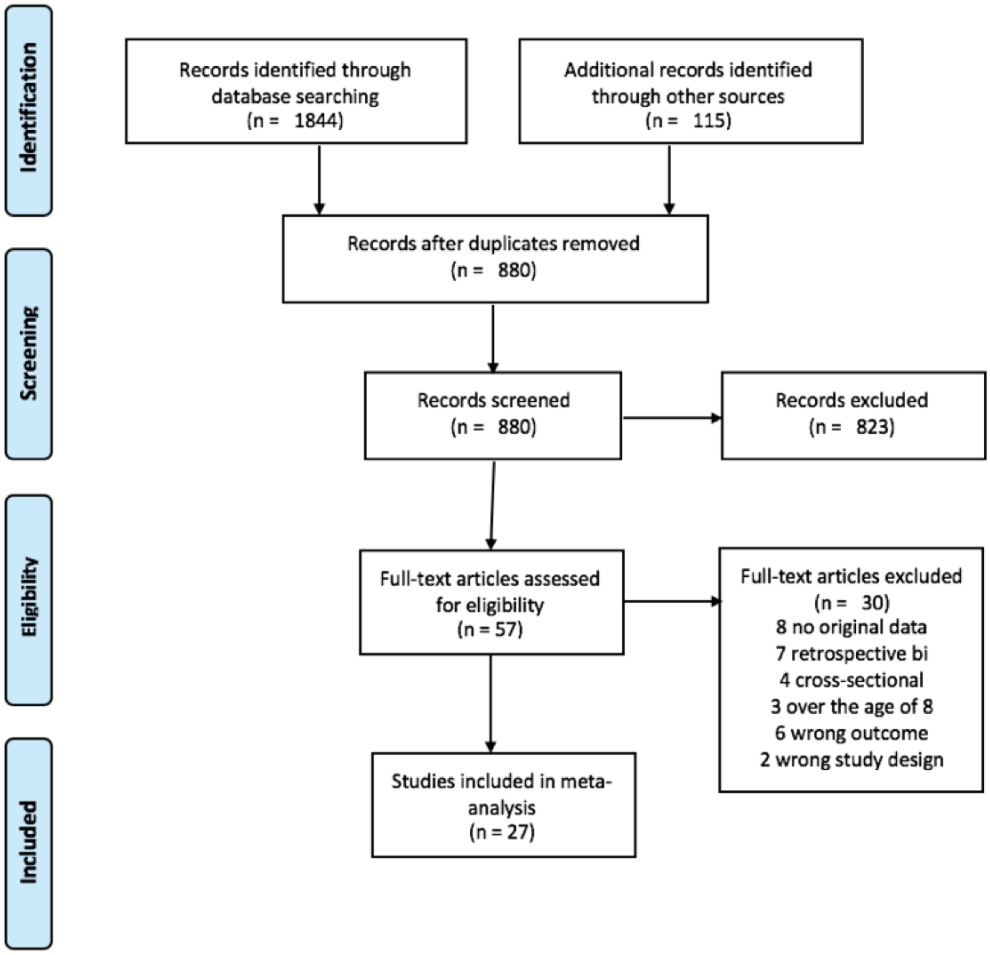
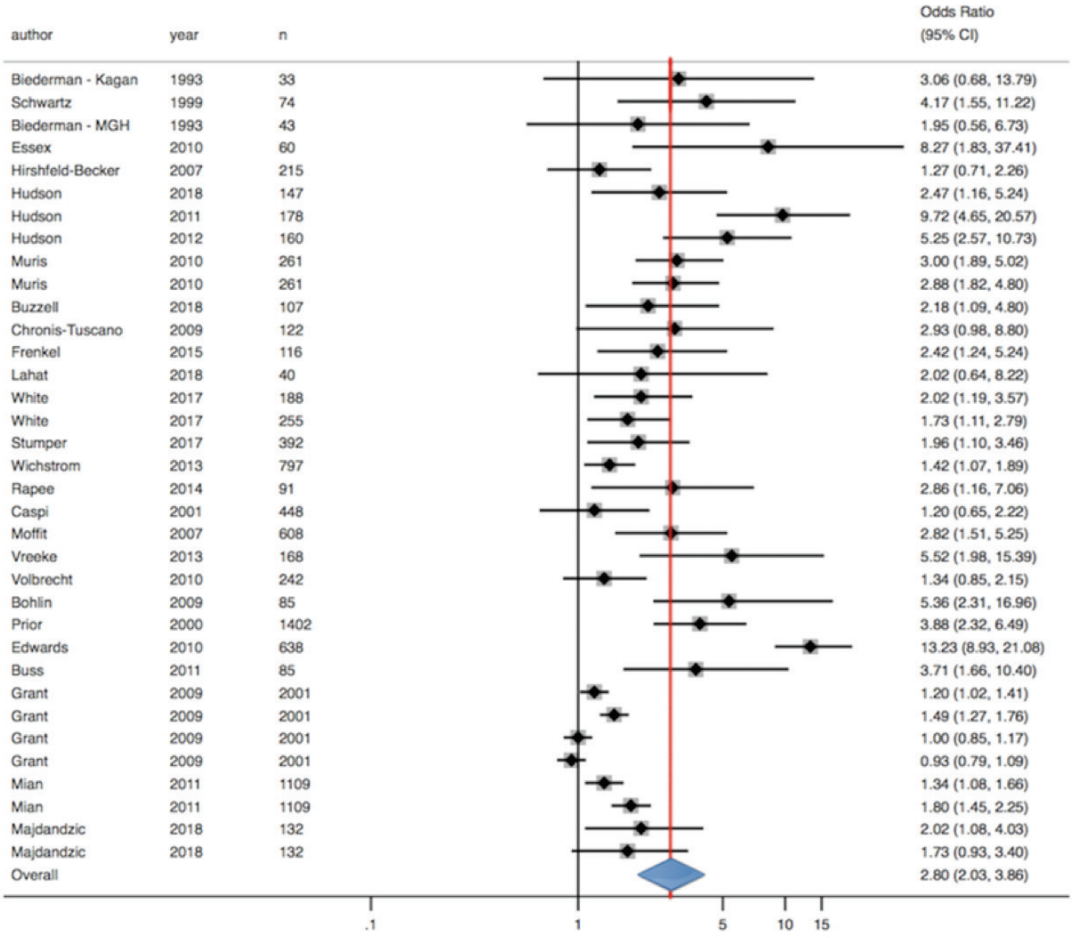
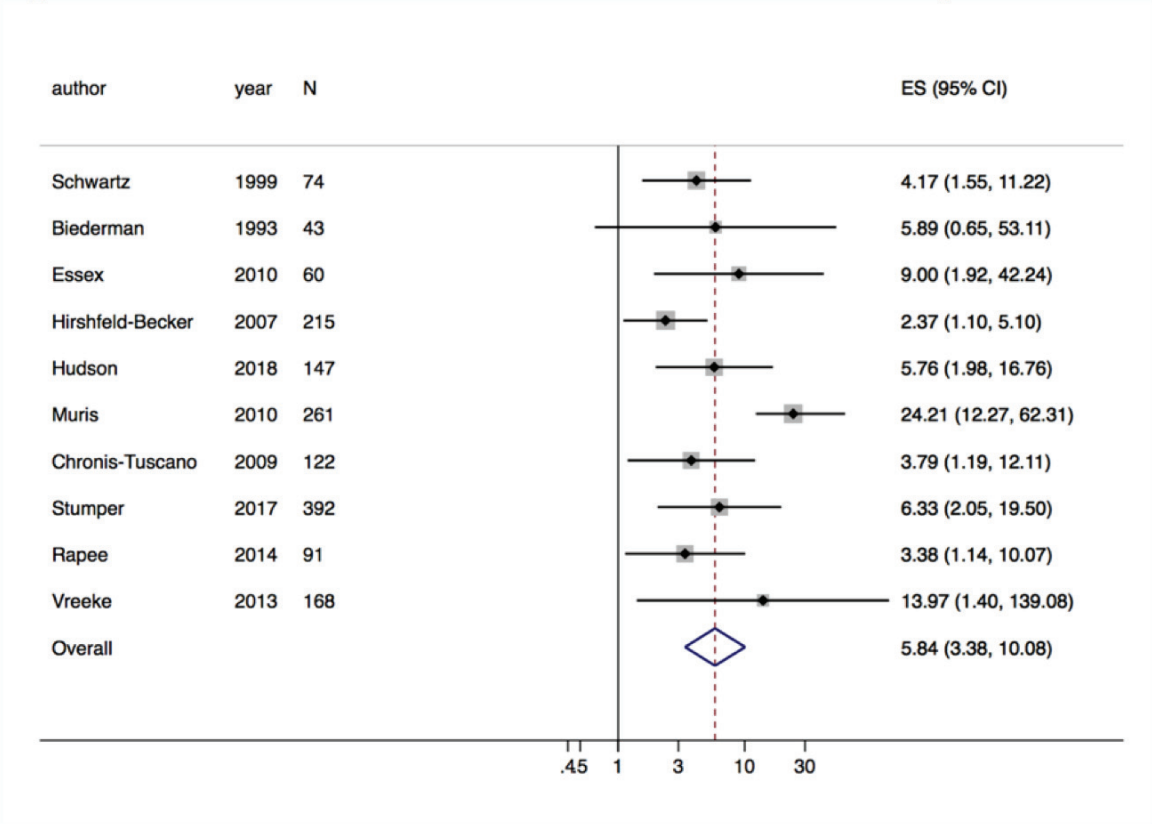


Figure 2.2.Behavioural inhibition in childhood and subsequent risk for anxiety.



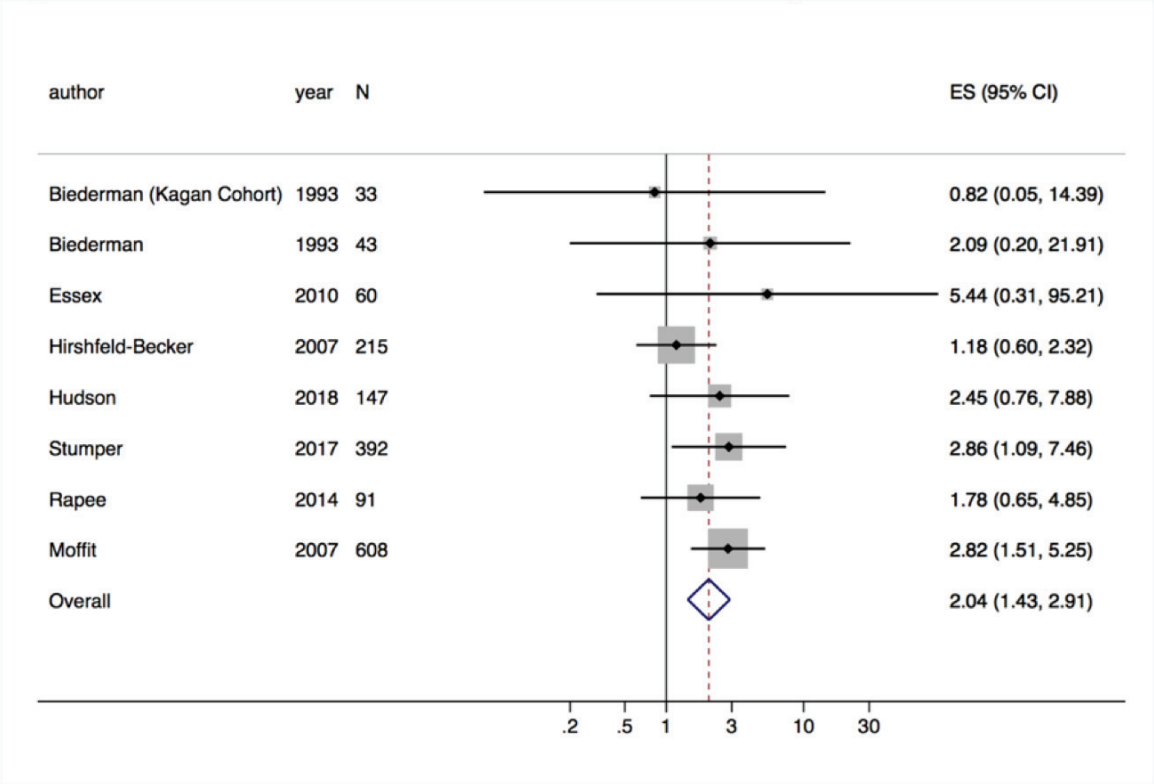
Note. The small black diamonds show the ORs of anxiety of individuals with behavioural inhibition compared to controls in each sample. The square around each estimate represents its weight in the meta-analysis. The horizontal black lines represent the 95% CIs of the estimates. Values to the right of the vertical black line indicate greater odds of anxiety in the group with BI. The red line indicates the overall OR for anxiety in individuals with BI compared to controls. The blue diamond represents the 95% CI of the overall OR.

Figure 2.3. Behavioural inhibition in childhood and the risk of subsequent SAD.



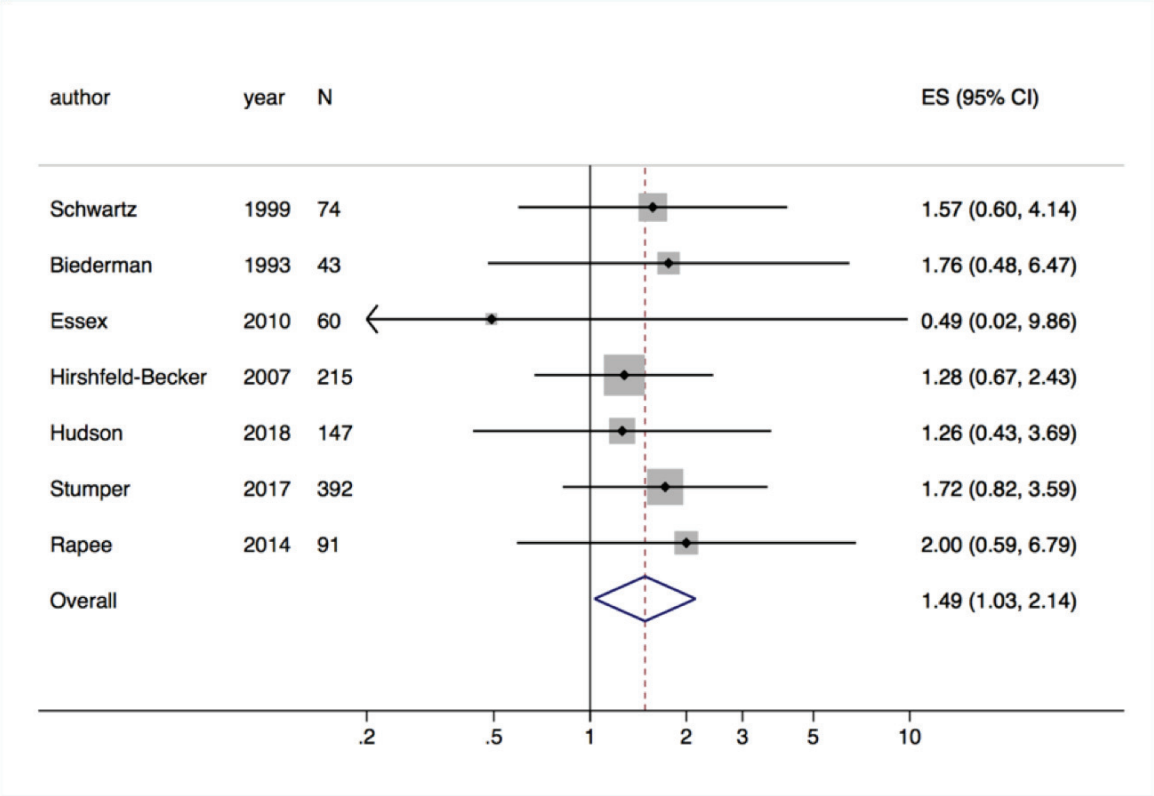
Note. The small black diamonds show the ORs of SAD of individuals with behavioural inhibition compared to controls in each sample. The black horizontal lines represent the 95% CIs of the estimate. The square around each estimate represents its weight in the meta-analysis. Values to the right of the vertical black line indicate greater odds of SAD in the group with BI. The dashed red line indicates the overall OR for SAD in individuals with BI compared to controls. The empty diamond represents the 95% CI of the overall OR.

Figure 2.4. Behavioural inhibition in childhood and subsequent risk of GAD.



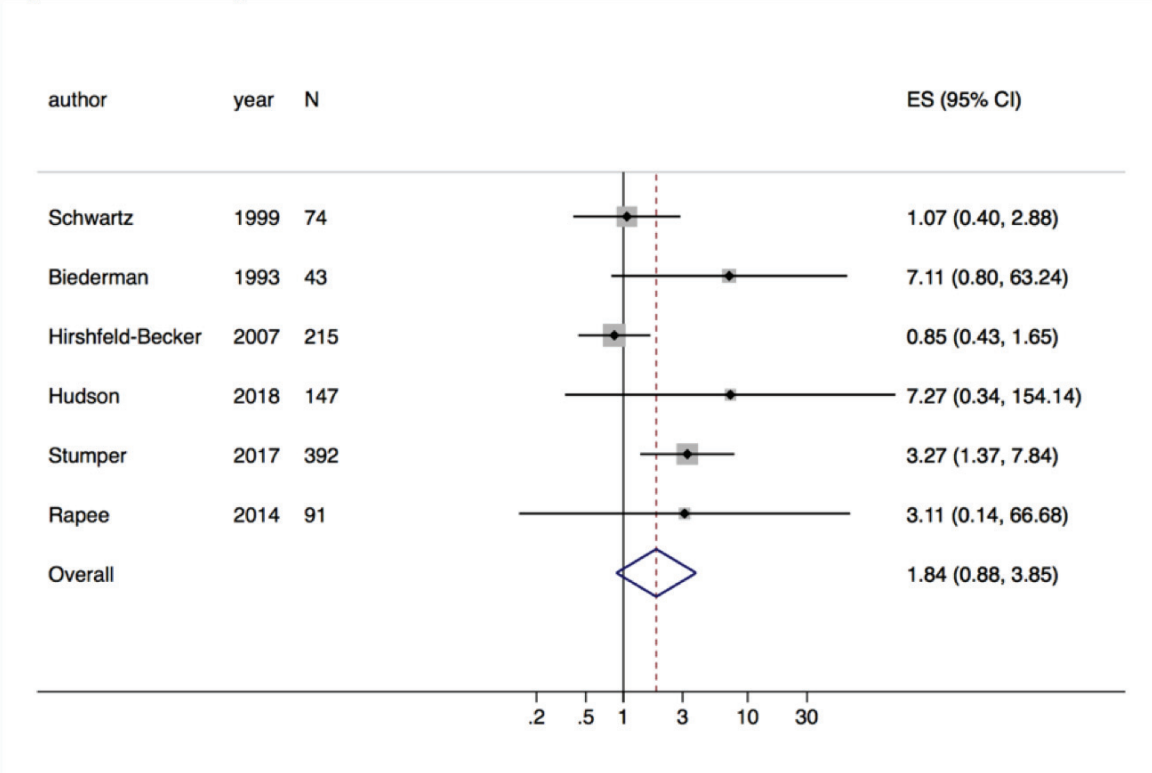
Note. The small black diamonds show the ORs of GAD of individuals with behavioural inhibition compared to controls in each sample. The black horizontal lines represent the 95% CIs of the estimate. The square around each estimate represents its weight in the meta-analysis. Values to the right of the vertical black line indicate greater odds of GAD in the group with BI. The dashed red line indicates the overall OR for GAD in individuals with BI compared to controls. The empty diamond represents the 95% CI of the overall OR.

Figure 2.5. Behavioural inhibition in childhood and the risk of subsequent specific phobia



Note. The small black diamonds show the ORs of specific phobia of individuals with behavioural inhibition compared to controls in each sample. The black horizontal lines represent the 95% CIs of the estimate. The square around each estimate represents its weight in the meta-analysis. Values to the right of the vertical black line indicate greater odds of specific phobia in the group with BI. The dashed red line indicates the overall OR for specific phobia in individuals with BI compared to controls. The empty diamond represents the 95% CI of the overall OR.

Figure 2.6. Behavioural inhibition in childhood and the risk of subsequent separation anxiety disorder



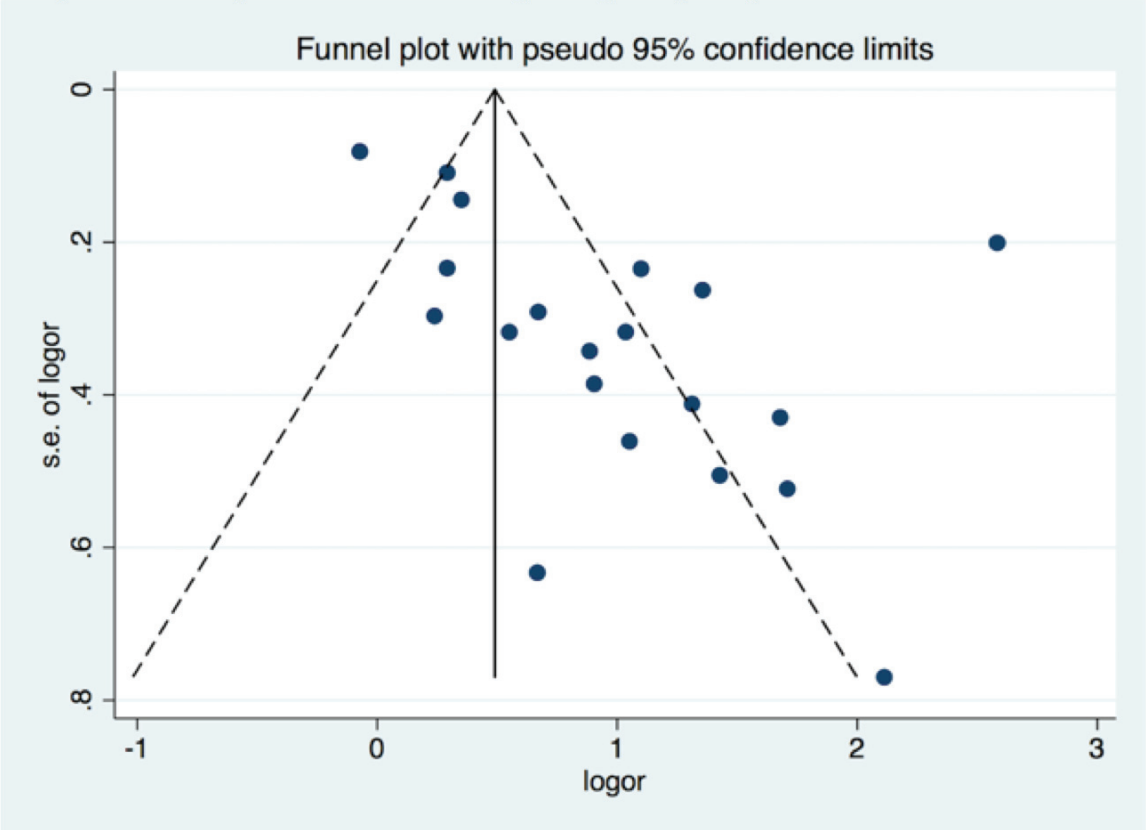
Note. The small black diamonds show the ORs of Separation Anxiety Disorder of individuals with behavioural inhibition compared to controls in each sample. The black horizontal lines represent the 95% CIs of the estimate. The square around each estimate represents its weight in the meta-analysis. Values to the right of the vertical black line indicate greater odds of Separation Anxiety Disorder in the group with BI. The dashed red line indicates the overall OR for Separation Anxiety Disorder in individuals with BI compared to controls. The empty diamond represents the 95% CI of the overall OR.

Based on meta-regressions, sex (*beta* = -0.004, CI -0.05 to 0.05, p=0.86), multiple BI assessments (*beta* = 0.42, CI -0.43 to 1.27, p=0.31), time delay between BI and anxiety assessments (*beta* = 0.006, CI -0.05 to 0.07, p=0.82), tool used to measure BI (*beta* = -0.28, CI -0.71 to 0.16, p=0.20) ,tool used to assess anxiety (*beta* = 0.09, CI -0.54 to 0.73, p=0.76), mean age at BI assessment (*beta* = 0.11, CI -0.04 to 0.26, p=0.15), mean age at anxiety assessment (*beta* =0.01, CI -0.05 to 0.07, p=0.69), geographical location (*beta* = -0.03, CI -0.28 to 0.21, p=0.78), year of publication (*beta* = -0.001, CI -0.03 to 0.03, p=0.94), group comparison (*beta* = -0.15, CI -0.48 to 0.78, p=0.62) or study quality (*beta* = 0.32, CI -0.04 to 0.68, p=0.08) had no significant effect on the relationship between BI and anxiety. See Table S2 in the supplement for details.

In the sensitivity analysis including only higher quality studies (scoring 3/5 or higher), the association between BI and anxiety was similar to that established in the primary analysis (OR= 3.05, 95% CI 2.18 to 4.25, p<0.001).

Visual inspection of the funnel plot, and Egger's intercept test (B= 3.51, 95% CI1.23 to 5.79, p= 0.005, **Figure 2.7**) suggested publication bias, however after restricting analysis to higher quality studies this effect was no longer significant (B= 1.27, 95% CI -2.04 to 4.58, p= 0.43).

Figure 2.7. Funnel plot of prospective association of BI and anxiety effect size by independent samples before restricting to higher quality studies



2.5 Discussion

BI in early childhood is associated with an almost threefold increase in odds of subsequent anxiety. This makes BI one of the strongest predictors of anxiety, which can be assessed very early in life, and adds to a large body of literature which supports a close relationship between inhibited temperament and anxiety (Rapee et al., 2009). The effect sizes established in the current study suggest BI is a stronger predictor of anxiety than other early risk factors including parenting behavior (Möller et al., 2016), early life stress (Lewis & Olsson, 2011), and maternal psychological distress (Kingston et al., 2015), and comparable to insecure attachment (Colonnesi et al., 2011) and parental anxiety (Micco et al., 2009). Identifying children with BI provides a unique opportunity to intervene early in order to reduce the risk of future anxiety and subsequent negative outcomes (Hirshfeld-Becker & Biederman, 2002).

Out of all anxiety disorders, SAD has the strongest relationship with BI. In line with a previous meta-analysis (Clauss & Blackford, 2012), our results support a close association between BI and social anxiety. We also established that BI was associated with an approximately two-fold increase in odds of GAD, and a one and a half-fold increase in odds of specific phobia. While BI increased the odds of subsequent separation anxiety to a similar degree, this relationship did not reach statistical significance. These findings are noteworthy, considering BI is often conceptualized as a risk factor specific to social anxiety. Our results suggest that early interventions for inhibited children may be particularly effective at reducing risk for SAD. However, such programs may also be beneficial at reducing risk of other anxiety disorders.

There are several possible explanations as to why BI is more strongly associated with SAD compared to other anxiety disorders. A recent twin study found that only social anxiety symptoms shared a significant amount of genetic factors with childhood BI (Bourdon et al., 2019). Therefore, the strong association found between BI and SAD may be due in part to a common genetic vulnerability. BI may also share more similarities with social anxiety compared to other anxiety disorders. For example, social avoidance and shyness are core characteristics of both BI and social anxiety that are not typical features of non-social anxiety disorders (American Psychiatric Association, 2013; Dyson et al., 2011; Rubin et al., 2009; Stein & Stein, 2008). Finally, the stronger association between BI and SAD may be due to the measurement of BI used in the included studies. As the social and non-social dimensions of BI are associated with different anxiety disorders (Dyson et al., 2011), it is not surprising that an instrument designed to assess social inhibition would be a stronger predictor of SAD. Therefore, the larger effect sizes found between BI and social anxiety in some past investigations may in part be attributed to the type of BI that was assessed. For example, the study by Muris and colleagues (2011) which found a stronger relationship between BI and SAD compared to BI and non-social anxiety disorders used a measure of inhibited temperament that only assessed the social aspect of BI.

To the best of our knowledge, this is the largest meta-analysis of the prospective relationship between BI and later anxiety, and the first to explore this association for a range of anxiety diagnoses. Our decision to only include studies which used a prospective design allowed us to establish the predictive value of BI for any anxiety, as well as for individual anxiety disorders. However, our study was not without limitations. First, we

found evidence of a systematic relationship between sample size and effect size. One explanation of this finding is publication bias, thus, smaller studies with non-significant effects may be less likely to be published. However, an alternative explanation is smaller studies may yield larger effect sizes for reasons unrelated to publication bias (e.g. higher quality) (Borenstein et al., 2009). To explore this alternative interpretation, we completed a sensitivity analysis restricting analysis to high quality studies. In this analysis we established an effect size very similar to that of our primary analysis and found no evidence of a relationship between sample size and effect size, suggesting that publication bias is unlikely to account for our original finding. Second, stable BI which persists across multiple assessments has been found to most strongly predict future anxiety (Chronis-Tuscano et al., 2009; Hirshfeld et al., 1992). We found that multiple BI assessments had no significant effect on the association between BI and anxiety in the meta-regression. However, only a small number of studies assessed BI more than once and it is possible that this result is due to insufficient power. Third, we identified moderate heterogeneity between studies. It is possible that the variation across studies may be due to different ratios of the various anxiety disorders in each sample, as we found that the strength of the association varies by type of anxiety disorder. In addition, it is possible that environmental factors such as overprotective parenting and parent psychopathology (Hudson et al., 2018; Ryan & Ollendick, 2018) influenced the association between BI and anxiety. However, as most previous investigations did not assess parent variables, we were unable to include them in the meta-regressions. Fourth, we were not able to assess the effect of comorbid diagnoses on the association between BI and anxiety given the available data. Fifth, we were not able to assess the association

between BI and panic disorder, agoraphobia, OCD or PTSD as they were not assessed in a sufficient number of studies. Future research should explore whether BI in childhood is associated with increased risk for these disorders.

Our study has important implications for prevention and early intervention for anxiety disorders. Cognitive behavioural interventions are effective at decreasing BI and anxiety in preschoolers (Howes Vallis et al., 2020). For example, a recent study of the efficacy of cognitive behavioural therapy (CBT) for young children with anxiety (Hirshfeld-Becker et al., 2010), found that 50% of children in the intervention condition were no longer considered inhibited at follow-up compared to only 10% of the control group. CBT interventions (Chronis-Tuscano et al., 2015; Lau et al., 2017) are also promising in the prevention of anxiety in inhibited children. Consequently, identifying children with BI and providing them with cognitive behavioural intervention may help prevent the onset of anxiety and its consequences, including poor academic, occupational and social functioning as well as comorbid psychiatric disorders (Kim-Cohen et al., 2003).

BI and anxiety are two closely associated but distinct constructs. As not all inhibited children go on to develop anxiety, the potential factors which influence this transition warrant future exploration. While some moderators such as parenting are well established (Hudson et al., 2018), the role of other factors is less clear. One area for future discovery is the extent to which the progression from BI to anxiety is due to genetic disposition, and how much of this transition is accounted for by environmental influences (Johnson et al., 2016a; Park et al., 2015; Talati et al., 2017). In addition, information processing of threats has been shown to moderate the association between BI

in early childhood and anxiety symptoms in adolescence (Barker et al., 2015; Henderson et al., 2015; White et al., 2017). Future research on cognitive and neural mechanisms that influence the transition from BI to anxiety diagnoses across the life course is necessary. In addition, future investigations should explore the impact of comorbid diagnoses on the relationship between BI and anxiety. Finally, as not every child with BI will develop anxiety, it will be important to determine what factors may promote resilience in inhibited children. This could inform clinical practice by identifying potential targets of preventative and intervention strategies for children with BI.

In conclusion, BI in early childhood is a strong risk factor for anxiety. As one in three children will have a diagnosable anxiety disorder before the age of 18 (Kessler et al., 2005), early preventive strategies are essential. Targeting children with high BI may help prevent the onset of anxiety disorders, and give these children the best chance to grow up healthy.

CHAPTER 3 BEHAVIOURAL INHIBITION IN OFFSPRING OF PARENTS WITH ANXIETY DISORDERS, MAJOR DEPRESSIVE DISORDER, AND BIPOLAR DISORDER

Contribution Statement

I drafted the manuscript, completed the data analysis, and devised the original idea for the chapter. I received guidance and editing from Dr. Barbara Pavlova, Dr. Lukas Propper, and Dr. Rudolf Uher. Data were collected by the FORBOW research team. I collected data, and assisted with the ongoing training of the laboratory assessment and clinical assessors. I designed and carried out coding of all data from the laboratory assessment used in this manuscript.

3.1 Abstract

Background: Behavioural inhibition, a temperament style characterized by fear and avoidance in the face of novelty, has been implicated as a risk factor for mood and anxiety disorders. Behavioural inhibition has been found to be associated with parental diagnosis of depression and anxiety disorders. However, further research is needed to quantify the strength of these associations. Furthermore, the relationship between behavioural inhibition and bipolar disorder is unclear. This study sought to explore the relationship between behavioral inhibition in offspring, and parent diagnosis of major depressive disorder, bipolar disorder and anxiety disorders.

Methods: We assessed behavioural inhibition through observation using the Laboratory Temperament Assessment Battery in 59 children between the ages of 3 and 6 who had a parent with major depressive disorder, bipolar disorder, an anxiety disorder or no history mental illness.

Results: Behavioural inhibition was nominally elevated, albeit not statistically significant, in offspring of parents with anxiety disorders compared to offspring of parents without anxiety disorders (OR = 3.30, 95% CI 0.80 to 13.66, $p = 0.10$). Compared to offspring of parents without mood disorders, behavioral inhibition was elevated in offspring of parents with depression, although once again this result was not statistically significant (OR = 1.84, 95% CI 0.52 to 6.52, $p = 0.345$). There was no association between behavioural inhibition and parent diagnosis of bipolar disorder (OR = 1.00, 95% CI 0.20 to 4.90, $p = 0.999$). When family history of mood and anxiety disorders was examined concurrently the association between behavioral inhibition and parental anxiety did not change (OR = 3.22, 95% CI 0.73 to 14.30, $p = 0.123$). Associations between

behavioral inhibition and parent diagnosis of major depressive disorder, and bipolar disorder were reduced.

Conclusions: Our findings provide tentative evidence that behavioural inhibition may be specifically associated with family history of anxiety disorders. Associations between behavioural inhibition and family history of mood disorders may in large be due to the presence of a comorbid anxiety disorder in parents. However, our sample size was small. If confirmed in a larger sample, early interventions which target behavioural inhibition in offspring of parents with anxiety disorders may prove beneficial.

3.2 Introduction

Mood disorders (i.e., major depressive disorder and bipolar disorder), and anxiety disorders often begin early in life, and have wide-reaching implications for health outcomes (Bandelow & Michaelis, 2015; Harvey, 2011; Kessler et al., 2005; Kim-Cohen et al., 2003; Nepon et al., 2010). Mood and anxiety disorders frequently co-occur, as up to 60% of people with major depressive disorder, and 50% of people with bipolar disorder also have a comorbid anxiety disorder (Fava et al., 2000; Pavlova et al., 2015). The presence of both a mood and anxiety disorders is associated with unfavourable outcomes (Goldberg & Fawcett, 2012; Schaffer et al., 2012). As mood and anxiety disorders are often chronic and affected individuals may never return to their prior level of functioning, intervening before disease onset may prove most beneficial. Thus, understanding the antecedents of mood and anxiety disorders is essential for early risk identification and intervention strategies (Sandstrom et al., 2019b). Given the high rates of comorbidity between mood and anxiety disorders, it may be important to study these risk factors concurrently.

Mood and anxiety disorders aggregate in families, thus children of parents with major depressive disorder, bipolar disorder, and anxiety disorders are at an increased risk to develop these diagnoses (Lawrence et al., 2019; Rasic et al., 2014). Furthermore, previous investigations suggest this risk extends beyond the specific disorder of the parent (Micco et al., 2009; Rasic et al., 2014). Thus, regardless of whether the parent has major depressive disorder, bipolar disorder or an anxiety disorder, their children are at increased risk for any mood or anxiety disorder. Given the shared vulnerability for mood and anxiety disorders identifying risk factors that are common across these disorder may

not only aid in the understanding of disease etiology, but also inform preventative and intervention strategies. Studies in offspring of parents with mood and anxiety disorders provide an opportunity to investigate the developmental precursors of major depressive disorder, bipolar disorder, and anxiety disorders in children known to be at high-risk for these disorders (Sandstrom et al., 2019b).

Studies of offspring of parents with mood and anxiety disorders typically focus on risk factors in later childhood and adolescence. However the earliest manifestations of risk for mood and anxiety disorders may be evident even before then. Identifying these risk indicators in offspring of parents with mood and anxiety disorders may allow for monitoring and preventative strategies at the earliest identifiable stage of risk. One early risk factor for mood and anxiety disorders may be behavioural inhibition.

Behavioural inhibition is a temperament style characterized by fear and avoidance in the face of novel stimuli, and is a strong risk factor for anxiety disorders (Clauss & Blackford, 2012). Previous research suggests that children of parents with depression and/or anxiety disorders are more likely to be classified as inhibited compared to children of parents without a mood or anxiety disorder (Hirshfeld-Becker et al., 2006; Rosenbaum et al., 2000; Rosenbaum et al., 1988). However, in these studies all parents with depression were initially included in a single group labelled “parents with major depression”. The separation of parents with major depressive disorder and bipolar disorder into two distinct groups was not done until a later study retrospectively analyzed the data to explore behavioural inhibition in offspring of parents with bipolar disorder (Hirshfeld-Becker et al., 2006). This raises concerns about the representativeness of the group of parents with major depression, and the generalizability of the findings. In

addition, previous research has largely focused on the relationship between behavioural inhibition and parent diagnosis of panic disorder/agoraphobia. As these two anxiety disorders are relatively rare (Kessler et al., 2006), previous findings may not be representative of the relationship between parental diagnosis of any anxiety disorder and behavioural inhibition in offspring. Thus, research which explores behavioural inhibition in offspring of parents with any anxiety diagnosis is needed. Finally, previous investigations have yielded inconsistent findings regarding whether parental anxiety (Rosenbaum et al., 1988) or parental depression (Rosenbaum et al., 2000) is a stronger predictor of behavioural inhibition in offspring. Therefore, clarification of the strength of the associations between behavioural inhibition and each familial high-risk group (i.e. anxiety, depression and bipolar) is needed.

The aim of the present study was to compare behavioural inhibition among offspring of parents with anxiety disorders, major depressive disorder, bipolar disorder, and no history of mental illness. Behavioural inhibition in offspring was measured using a laboratory assessment. We hypothesized behavioural inhibition would be elevated in offspring of parents with mood and anxiety disorders compared to the control group. It is currently unclear whether behavioural inhibition is more strongly associated with parental diagnosis of mood disorders or parental diagnosis of anxiety disorders. However, given the large body of literature supporting a close relationship between behavioural inhibition and anxiety (Rapee, 2014; Rapee et al., 2009; Rapee & Coplan, 2010), we predicted family history of anxiety disorders would be a stronger predictor for behavioural inhibition in offspring than family history of mood disorders.

3.3 Methods

3.3.1 Participants

Participants were offspring from the Families Overcoming Risks and Building Opportunities for Wellbeing project (FORBOW; Uher et al., 2014). FORBOW is a prospective longitudinal familial high-risk cohort study of offspring of parents with major depressive disorder, bipolar disorder, anxiety disorders, schizophrenia, and no history of mood, anxiety or psychotic disorders (controls). Families with mood and psychotic disorders were enrolled in the study through affected parents receiving treatment at inpatient and outpatient psychiatric services in Nova Scotia, where clinicians inquired whether patients had biological children in the eligible age range. Offspring in the eligible age range were enrolled irrespective of whether any psychopathology was present. Anxiety disorders in parents with mood and psychotic disorders were identified at the baseline FORBOW assessment. Control offspring were enrolled through schools in the same geographic location as where the high-risk offspring were recruited. Inclusion criteria were at least one biological parent was available for assessment and offspring were between 1 and 27 years of age. In some cases, mood and anxiety disorders were identified in parents initially recruited as controls at the baseline FORBOW assessment. These families then became part of the parental anxiety disorders group, parental major depressive disorder group, or parental bipolar disorder group.

Participants in FORBOW complete annual assessments that measure a variety of factors related to youth development and mental health. Offspring were eligible for the current study if they had a parent with major depressive disorder, bipolar disorder, an anxiety disorder, or no history of mood, anxiety and psychotic disorders, if they were

between 3 and 6 years of age, if they had completed at least one laboratory assessment, and were fluent in English or French. Participants were excluded if they had a diagnosis of autism spectrum disorder (n=2), as the inclusion of these children would have made the results difficult to interpret. Furthermore, to my knowledge the use of the Preschool Laboratory Temperament Assessment Battery (Lab-TAB; Goldsmith et al., 1995) in children with autism has not been validated.

The study protocol was approved by the Nova Scotia Health Authority Research Ethics Board. The parent or guardian provided written informed consent for the child, and the child gave verbal assent.

3.3.2 Diagnostic Assessment

Parent diagnosis was established using the *Schedule for Affective Disorders and Schizophrenia* (SADS-IV) (Endicott & Spitzer, 1979) and the *Structured Clinical Interview for DSM 5 Disorders* (SCID-5) (First et al., 2015). All diagnoses were confirmed during consensus meetings with psychiatrists blind to child psychopathology.

3.3.3 Laboratory Assessment.

All children in this study took part in at least one laboratory visit which lasted approximately two hours. As FORBOW is a longitudinal study with assessments occurring yearly some children completed the laboratory visit multiple times (mean number of visits =1.7).

During the laboratory visit 11 episodes from the Lab-TAB (Goldsmith et al., 1995) were administered. The Lab-TAB (Goldsmith et al., 1995) is a comprehensive observational measure designed to assess children's temperament in a laboratory setting. The Lab-TAB episodes are modeled after everyday situations and designed to elicit

specific emotions and behaviors representative of different temperament dimensions. Previous research has established the Lab-TAB has strong predictive and ecological validity, and has linked temperament measured using the Lab-TAB with developmental and psychiatric outcomes later in childhood (Dougherty et al., 2013; Durbin et al., 2007; Dyson et al., 2011; Lo et al., 2014; Olino et al., 2010).

After each episode children took breaks before starting the next episode in order to return to a neutral state. The entire assessment was video-recorded using two cameras placed at different locations in the assessment room, and these recording were later coded.

The three episodes used to measure behavioural inhibition in the current study were the risk room episode, the stranger approach episode, and the jumping spider episode. These episodes were selected based on previous research which has used these episodes or very similar tasks to assess behavioural inhibition (Johnson et al., 2016b; Olino et al., 2010; Rosenbaum et al., 2000). The three tasks are described in more detail below.

Risk Room. In this episode the child is allowed to explore and play with a set of novel toys including a black box with a hole in it and a scary face drawn on, a wolf mask, a balance beam, a tunnel, and a two-step stool and gym mat.

Stranger Approach. The stranger approach assesses the child's social fear when they are left alone in the test room and confronted with an unfamiliar slightly intimidating person who attempts to engage the child in conversation while slowly moving closer to the child. This episode is modeled after "real-life" events where children may be confronted with strangers, such as riding the bus or playing at the park.

Jumping Spider. This episode is designed to elicit a startle or fear reaction from the child based on an unexpected event. In this episode the experimenter shows the child a toy spider in a box. The experimenter opens the box to reveal the spider before prompting the child to pet the spider. When the child complies, the experimenter makes the spider jump using a cord attached to spider, which is kept hidden from the child. This is repeated four times or until the child refuses to touch the spider again. After the four trials or refusal to touch the spider again, the experimenter explains to the child that the spider is just a toy and shows the child how the spider works. The child is allowed to touch/play with the spider if they want too.

3.3.4 Coding Procedures.

Coding schemes were designed using recommendations from Goldsmith et al. (1995) and variables which have been used in previous work with the Lab-TAB (Durbin et al., 2005; Johnsonet al., 2016b; Olino et al., 2010; Rosenbaum et al., 2000). Coders were trained by a "master coder" and were kept blind to the ratings of the other coders.

The coding of each episode was broken down into epochs, and the child's maximum intensity for each variable was coded during each individual epoch. The risk room epochs lasted 20 seconds, the stranger approach epochs lasted 10 seconds, and for jumping spider each trial represented an individual epoch. After each video was coded, a summary score for each variable in the episode was calculated. Variables coded across all three episodes were facial, body and vocal fear. Additional variables coded in the risk room were time to touch each object, number of objects touched, tentative play, references to parent, proximity to parent, references to experimenter, and time spent playing. Additional variables from the stranger approach were approach to, and avoidance of the stranger,

verbal/nonverbal interactions with the stranger, and gaze aversion. In the jumping spider episode other coded variables were approach, and withdrawal from the spider, startle, and gaze aversion. It was also noted whether the child played with the spider at the end of the episode when given the opportunity by the experimenter. See appendix C for full breakdown of all coded variables.

3.3.5 Data Analysis Plan

For the risk room, jumping spider and stranger approach episodes an overall rating of behavioural inhibition was computed. Each individual variable was averaged across all epochs and divided by the highest possible score on that variable (i.e. for facial fear the highest score in each epoch was 3 therefore the average on facial fear for each participant was divided by 3). Thus, each variable had a value ranging from 0 to 1. All variables were then summed and divided by the total number of variables to give a rating of inhibition ranging from 0 to 1 for each episode. The rating of behavioural inhibition from each episode was then z-scored. Children were considered inhibited if they scored one standard deviation above the z-scored mean of the control group on any one of the episodes; risk room, stranger approach or jumping spider. Thus, children were classified into two groups (0=uninhibited, 1=inhibited).

To establish inter-rater reliability between different raters at least 20 videos from the jumping spider and stranger approach episodes were double rated. While I initially intended to also establish inter-rater reliability for the risk room, I was unable to given that Nova Scotia declared a state of emergency due to the SARS-CoV-2 virus on March 22nd 2020 and the second rater was unable to continue working. We established inter-rater reliability using intra-class correlation (ICC), which is a measure of interrater

agreement between two unique raters. We sought to obtain an ICC value above 0.6 which would indicate that the agreement between the two coders is sufficient (Koo & Li, 2016).

The dependent variable in all analyses was offspring's behavioral inhibition. The independent variables were parent diagnosis of anxiety disorders, and parent diagnosis of mood disorders. I first examined these independent variables separately. For the analysis of the effect of parental anxiety, parent diagnosis was classified into two group: 1) no anxiety disorder, or 2) anxiety disorder. To examine the effect of family history of mood disorders, parent diagnosis was classified into three groups: 1) no history of major mood disorders, 2) family history of major depressive disorder, or 3) family history of bipolar disorder. Each familial high risk group was compared to the control group. Next I included parental anxiety as an additional predictor in the analysis exploring the association between family history of mood disorders, and behavioural inhibition. This allowed us to partial out the unique effect each parental diagnoses had on behavioural inhibition. I examined the effect of parent diagnosis on behavioural inhibition using mixed-effects logistic regressions fitted in the generalized linear latent and mixed model (GLLAMM) framework. This allowed for the inclusion of multiple observations from the same individual, and accounted for the non-independence of assessments from related individuals from the same family with nested random effects of family and individual.

In all of our analyses we controlled for age, time point (i.e., which assessment year the child was in), and sex as covariates. We report the effect size of comparisons as odds ratio (OR) with their 95% confidence intervals (CI). ORs reflected the probability of behavioural inhibition based on parent diagnoses. ORs greater than 1 represent an increased likelihood of behavioural inhibition in offspring of parents with major

depressive disorder, bipolar disorder, or anxiety disorders compared to offspring of control parents. We consider all results with $p < 0.05$ as significant.

This investigation was part of a larger on-going project and data collection had to be halted in March 2020 because of restrictions on contact with research participants in the context of the COVID-19 pandemic. To help interpret both positive and negative results in the context of limited sample size, I completed a post-hoc power calculation. I based the power analysis on effect sizes observed in the current study from the regression which included both family history of anxiety disorders, and family history of mood disorder, as this was the study's primary research question. In order to inform future research and analysis done in this sample I also calculated how many additional participants would need to be recruited to achieve a power of 0.80 (Columb & Atkinson, 2016; Hickey et al., 2018).

3.4 RESULTS

3.4.1 Interrater Reliability

For the stranger approach episode a total of 38 videos were double rated. Agreement between the two raters was moderate with an ICC of 0.60. For the jumping spider episode a total of 21 videos were double rated and the ICC was 0.92, suggesting the inter-rater relatability was excellent.

3.4.2 Demographic Characteristics

We included 59 participants from 54 families. On average participants had completed 1.7 assessments equalling 98 observations in total. In all 59 offspring we had information on mother's diagnosis, we had information on father's diagnosis in 45 offspring. The sample was composed of 19 offspring of a parent with major depressive disorder (15 with a comorbid anxiety disorder), 17 offspring of a parent with bipolar disorder (12 with a comorbid anxiety disorder), 8 offspring of parents with an anxiety disorder without a comorbid mood disorder and 15 control offspring. Of the 35 offspring who had a parent with an anxiety disorder, 22 had a parent with generalized anxiety disorder, 17 had a parent with social anxiety disorder, 1 had a parent with panic disorder, 8 had a parent with post-traumatic stress disorder, and 2 had a parent with obsessive compulsive disorder. The average age of participants was 4.66 (SD= 1.32), and our sample was composed of more females than males (38.98% males). 17 children were classified as inhibited on at least one assessment. Full demographic characteristics by parent diagnosis are displayed in **Table 3.1**.

3.4.3 Primary Analysis

One child was classified as inhibited based on the risk room episode. Sixteen children were classified as inhibited based on the stranger approach episode, and two of these children were classified as inhibited on two assessments. No child was classified as inhibited based on the jumping spider episode. There were no children who were classified as inhibited on more than one of the episodes.

Compared to offspring of parents without anxiety disorders, offspring of parents with anxiety disorders were more likely to be classified as inhibited at trend level (OR = 3.30, 95% CI 0.80 to 13.66, $p = 0.10$; see **Figure 3.1**). Behavioral inhibition was nominally more common, albeit not statically significant, in offspring of parents with major depressive disorder compared to offspring of parents without a mood disorder (OR = 1.84, 95% CI 0.52 to 6.52, $p = 0.345$; see **Figure 3.2**). There was no difference in rates of inhibition between the comparison group and offspring of parents with bipolar disorder (OR = 1.00, 95% CI 0.20 to 4.90, $p = 0.999$; see **Figure 3.2**).

When parental anxiety and parental mood disorders were entered into the regression equation together the association between parental anxiety and behavioural inhibition remained almost the same (OR = 3.22, 95% CI 0.73 to 14.30, $p = 0.123$), while the associations between parental depression (OR = 1.14, 95% CI 0.30 to 4.34, $p = 0.847$) and parental bipolar disorder (OR = 0.69, 95% CI 0.13 to 3.70, $p = 0.666$) were reduced. See **Table 3.2** for full results from each regression. See **Figure 3.3** for the rates of inhibition by parental diagnosis.

3.4.4 Post-Hoc Power Analysis

The current study had a power of 0.52. In order to increase the power to 0.80 the analysis would need to include an additional 62 participants, equalling 121 participants in total.

Table 3.1. Demographic characteristics of offspring by parent diagnosis

Parent Diagnosis	Control	Anxiety	Depression	Bipolar
N	15	8	19	17
Age M (SD)	4.65 (1.34)	4.63 (1.27)	5.01 (1.17)	4.38 (1.29)
Sex (% males)	3 (20)	3 (38)	10 (53)	7 (41)
Inhibited N (% inhibited)	2 (13)	3 (38)	6 (32)	6 (35)

Note. N= number, M= mean, SD= standard deviation. For offspring of parents with depression 79% had a parent with both depression and anxiety. For offspring of parents with bipolar disorder 71% had a parent with both bipolar disorder and anxiety.

Table 3.2. Regression models predicting behavioural inhibition in offspring of parents with different diagnoses

Models		Analysis		
		Odds Ratio	95% CI	P-value
Model 1: Comparison of offspring of parents with and without anxiety disorders		3.30	0.80-13.66	0.100
	Covariates			
	Age	0.44	0.20-0.99	0.046
	Sex	0.65	0.15-2.90	0.572
	Time Point	1.40	0.83-2.38	0.203
Model 2: Comparison of offspring of parents with and without mood disorders	Parental Depression	1.84	0.52-6.52	0.345
	Parental Bipolar Disorder	1.00	0.20-4.90	0.999
	Covariates			
	Age	0.46	0.21-0.98	0.045
	Sex	0.73	0.17-3.10	0.674
	Time Point	1.36	0.83-2.25	0.22
Model 3: Unique contribution of parental anxiety, parental depression, and parental bipolar disorder	Parental Anxiety	3.23	0.73-14.30	0.123
	Parental Depression	1.14	0.30-4.33	0.847
	Parental Bipolar Disorder	0.69	0.13-3.70	0.666
	Covariates			
	Age	0.43	0.19-0.97	0.041
	Sex	0.69	0.15-3.09	0.623
	Time Point	1.43	0.84-2.41	0.187

Note. CI= confidence interval.

Figure 3.1. Percentage of offspring of parents with and without anxiety disorders with behavioural inhibition

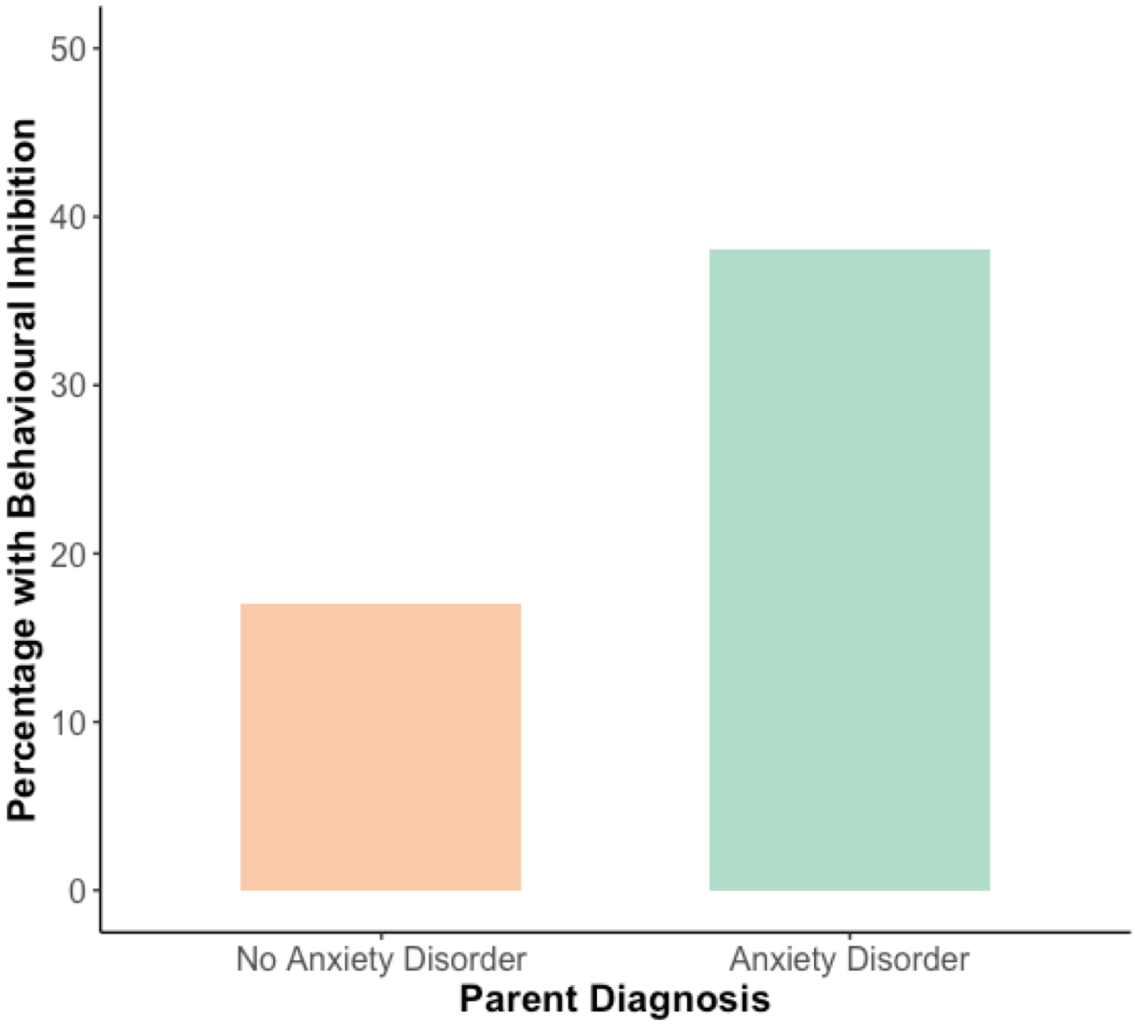


Figure 3.2. Percentage of offspring of parents with and without mood disorders with behavioural inhibition

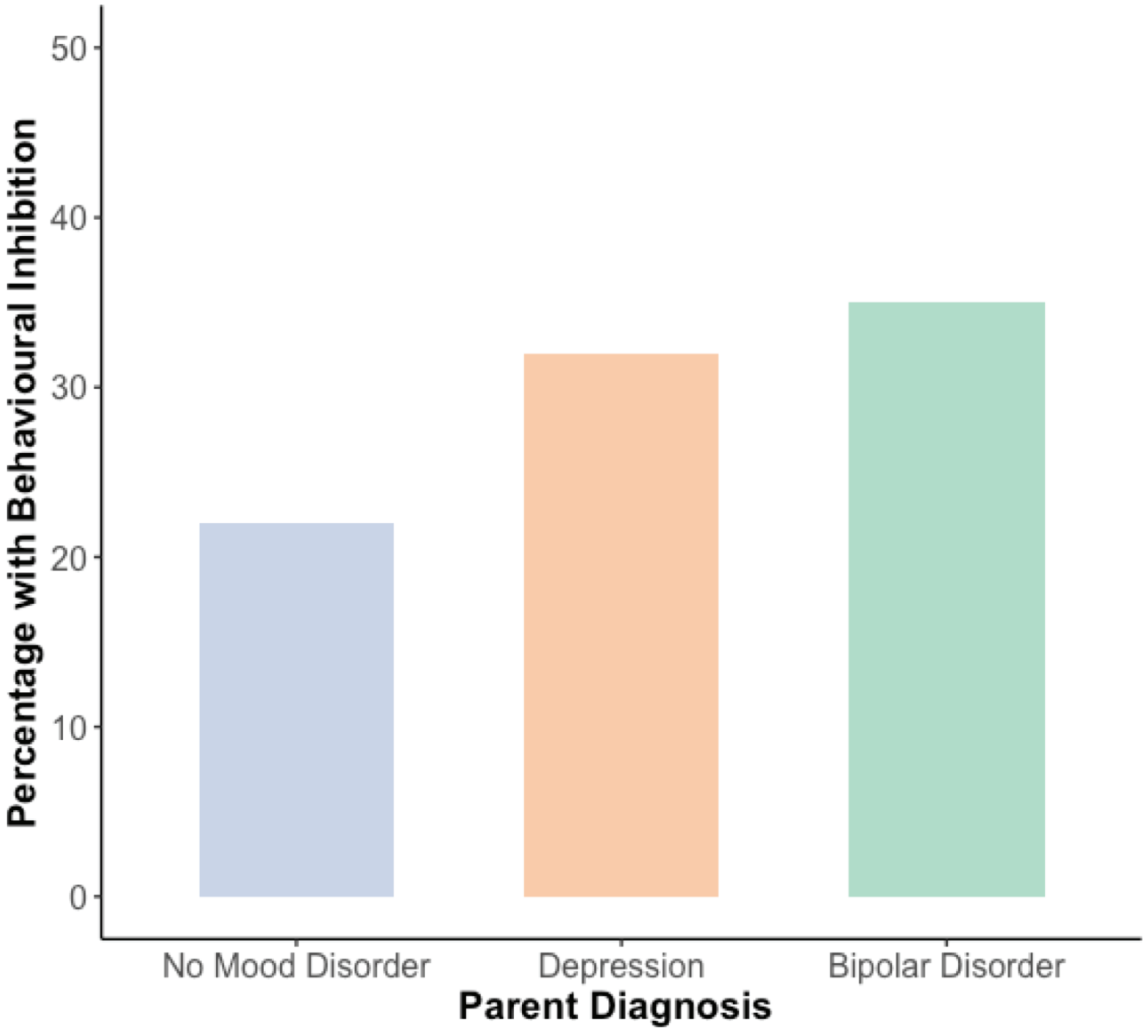
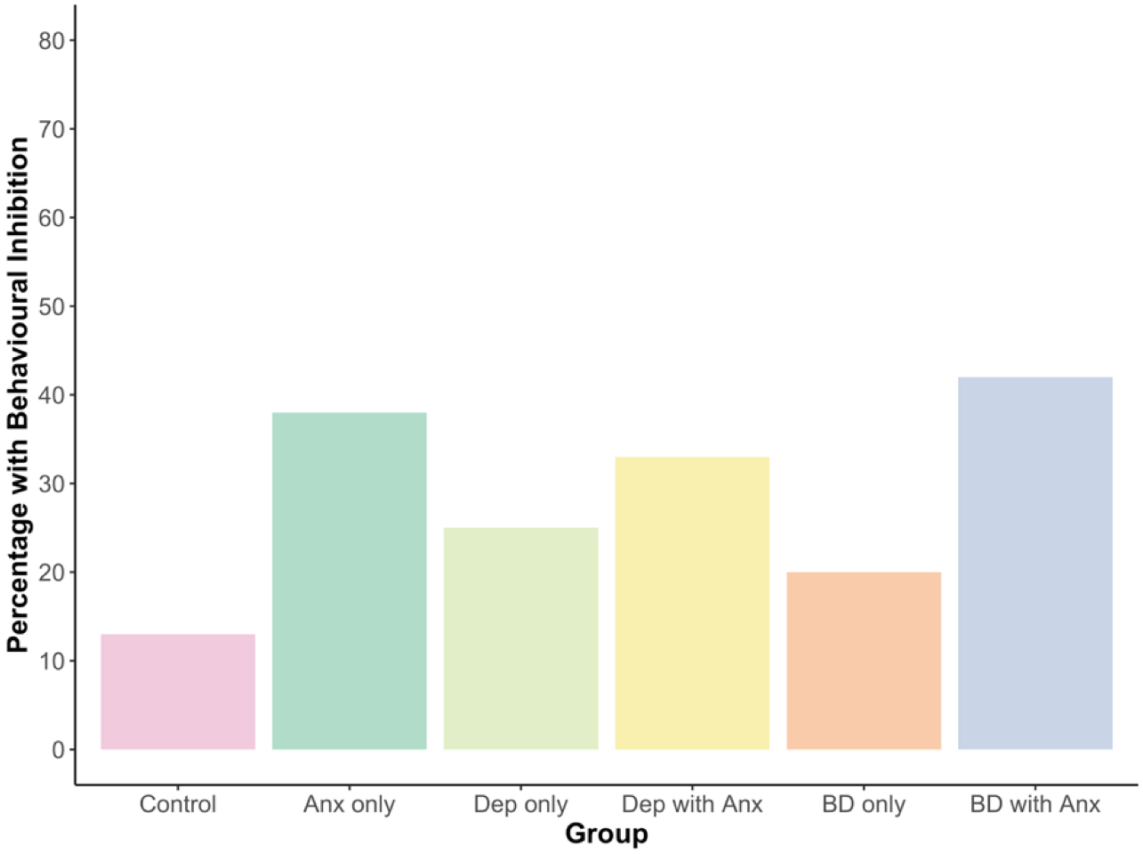


Figure 3.3. Percentage of offspring with behavioural inhibition by parental mood and anxiety diagnoses



Note. Control= no mood or anxiety disorder, Anx only= Anxiety disorder only, Dep only= Depression only, Dep with Anx= Depression with comorbid anxiety disorder, BD only= Bipolar Disorder only, BD with Anx= Bipolar disorder with comorbid anxiety disorder.

3.5 Discussion

3.5.1 Summary of Findings

We found no statistically significant differences in behavioural inhibition in any of the high-risk groups compared with controls. It is likely the small sample size of the present study limited our ability to detect statistically significant differences between groups. Despite not reaching statistical significance, the effect size for the relationship between parental anxiety and inhibition was large, as offspring of parents with anxiety disorders were at a more than threefold increase in odds for behavioural inhibition compared to offspring of parents without anxiety disorders. Furthermore, behavioural inhibition was also numerically elevated in offspring of parents with depression, although once again this result was not statistically significant. The rate of behavioural inhibition in offspring of parents with bipolar disorder was equivalent to that of the comparison group. When the effect of parental diagnosis of mood and anxiety disorders was explored concurrently, anxiety disorders in parents accounted for a large portion of the previously observed associations between behavioural inhibition and parental mood disorders.

Our finding that behavioural inhibition was nominally higher in offspring of parents with anxiety disorders is consistent with previous research which found elevated rates of behavioural inhibition in offspring of parents with panic disorder/agoraphobia (Rosenbaum et al., 2000; Rosenbaum et al., 1988). Taken together, these findings support a strong relationship between family history of anxiety disorders and behavioural inhibition in offspring.

Behavioural inhibition was nominally higher, albeit not statistically significant, in offspring of parents with depression compared to offspring of parents with no history of

mood disorders. Previous research has found children of parents with depression are significantly more likely to be classified as inhibited with similar odds ratios to that found in our study (Kochanska, 1991; Rosenbaum et al., 2000). Therefore, it is likely the lack of a significant association between behavioural inhibition and parental diagnosis of depression in the present study was due to low power. Future research with a larger sample size is needed to better elucidate the relationship between behavioural inhibition and family history of major depressive disorder. Furthermore, I did not excluded parents with anxiety disorders from the comparison group in the analysis of the effect of family history of mood disorder on behavioral inhibition. Thus, it is possible that the presence of anxiety disorders in parents with no history of mood disorders increased the rate of behavioral inhibition in this group relative to that in the group of offspring of parents with depression.

We found that behavioural inhibition did not differ in offspring of parents with bipolar disorder compared to offspring of parents without a mood disorder. This is consistent with a previous investigation which found no difference in rates of inhibition between offspring of mothers with bipolar disorder and offspring of mothers with no history of mental illness (Kochanska, 1991). Our results are also in line with findings from the study by Hirshfeld-Becker and colleagues (2006), which found behavioural inhibition did not differ between offspring of parents with and without bipolar disorder (Hirshfeld-Becker et al., 2006). When comorbid anxiety disorders in parents were controlled for behavioural inhibition was less common, although non-significant, in offspring of parents with bipolar disorder compared to controls.

Taken together with past research our findings provide tentative evidence that family history of bipolar disorder may not be associated with behavioural inhibition in offspring.

When the effect of parental diagnosis of mood and anxiety disorders was explored concurrently, the odds ratio for behavioural inhibition in offspring of parents with anxiety disorders remained almost the same, whereas the odds ratios for behavioural inhibition in offspring of parents with mood disorders were reduced. This suggests that parental anxiety disorders accounted for some of the previously observed associations between parental mood disorders and behavioural inhibition. This study is the first to explore the unique contribution of parental anxiety and parental mood disorders to behavioural inhibition. While previous investigations suggest behavioural inhibition is highest in offspring of parents with both a mood and anxiety disorder (Rosenbaum et al., 2000; Rosenbaum et al., 1988), our findings suggest it is presence of an anxiety disorder in the parent which is driving this association. If our results are replicated in future research it would suggest that familial transmission of behavioural inhibition can largely be attributed to parental anxiety disorders.

Interestingly, after controlling for parental anxiety, family history of bipolar disorder was associated with lower rates of behavioural inhibition compared to the control group, although this difference was not statistically significant. This finding is in line with the theoretical framework that suggests parental diagnosis of bipolar disorder may be more closely associated with behavioural disinhibition, which exists at the opposite end of the response to novelty spectrum than behavioural inhibition (Hirshfeld-Becker et al., 2003).

There are several possible explanations as to why behavioural inhibition may be more strongly associated with parental diagnosis of anxiety disorders compared with parental diagnosis of mood disorders. First, behavioural inhibition and anxiety disorders may share more genetic variants compared to behavioural inhibition and mood disorders. This is supported by a previous investigation which established significant overlap in the genetic influences for behavioural inhibition and anxiety (Bourdon et al., 2019). Second, overprotective parenting has been proposed to be associated with behavioural inhibition (Johnson et al., 2016b). Parents with low overprotective parenting behaviors may be more likely to allow their children to be exposed to novel situations which in turn can facilitate the development of adaptive coping strategies in children, leaving them better equipped to manage novel, anxiety-provoking situations in the future (Johnsonet al., 2016b). On the other hand, parents with high overprotective parenting behaviors are more likely to shelter their children from novelty. This may interfere with the child's acquisition of necessary coping strategies, increasing the risk they will exhibit fear in the face of novelty in the future. While overprotective parenting has previously been found to be elevated in both parents with mood and anxiety disorders (Gomes et al., 2015; Hudson et al., 2018), there is some evidence to suggest it may be more strongly associated with parental anxiety (Clarke et al., 2013). Thus, the stronger association between behavioural inhibition and parental anxiety compared to the associations between behavioural inhibition and parental mood disorders may in part be due to greater exposure to overprotective parenting in offspring of parents with anxiety disorders.

3.5.2 Study Strengths

Our study benefits from careful selection and separation of parents with mood disorders into two distinct groups, one composed of parents with major depressive disorder, and the other composed of parents with bipolar disorder, which increases the generalizability of our findings. In addition, parent diagnosis was established using rigorous in-person diagnostic interviews, and all diagnoses were confirmed by psychiatrists, which increases the reliability and validity of diagnoses made in this study (Barriball & While, 1994; First et al., 2015). The use of an observational measure of temperament, which was rated by video-coders blind to parents' mental health, was also a strength as we were able to assess behavioural inhibition independent of parental bias (Maoz et al., 2014; Sandstrom et al., 2019a).

3.5.3 Study Limitations

Our findings should be interpreted in the context of several limitations. First, the sample size of this study was not large, which limited our power to detect statistically significant differences between groups. Based on post-hoc power analysis there was a 48% chance that a significant effect between groups would not be detected when in fact this difference did exist. Therefore, it is likely that at least some of the non-significant findings in this study are the result of type II error. Future research in a larger sample is needed. Second, while a number of children did complete the laboratory assessment in multiple years, there were some children who only completed one assessment. Therefore, we were unable to look at the stability of behavioural inhibition over time, and whether this was associated with family history of mood and anxiety disorders. Stable behavioural inhibition which persists across multiple assessments has been found to most strongly

predict later psychiatric disorder (Hirshfeld et al., 1992). Thus, it is possible that enduring behavioural inhibition which persists through development may be more strongly associated with family history of mood and anxiety disorders. Third, our sample was composed of primarily Caucasian children which limits the generalizability of our findings. Previous research suggests that behavioural inhibition may vary across ethnic background (Vreeke et al., 2012). Thus, future research in a more diverse population is needed to determine whether ethnicity and racial background influence associations between behavioural inhibition and family history of mood and anxiety disorder. Fourth, based on previous research that suggested behavioural inhibition may differ according to parent diagnoses (Hirshfeld-Becker et al., 2006; Rosenbaum et al., 2000; Rosenbaum et al., 1988), I initially intended to use data from a large normative sample to determine the cut-offs for inhibition on the Lab-Tab episodes. However, I was unable to obtain this data. Therefore, the cut-offs used in this study were based on our control group. Given that this group was small it is possible that these estimates of inhibition were unreliable (Bridges & Holler, 2007).

3.5.4 Future Directions

Our study has important implications for future research. First, and most importantly, there is a need for replication in studies with large sample sizes. All existing research on behavioural inhibition in offspring of parents with major depressive disorder, bipolar disorder, and anxiety disorders has been done with small sample sizes. Low power makes it difficult to conclude whether behavioural inhibition is associated with parent diagnosis of mood and anxiety disorders. Second, longitudinal studies are needed to establish the prospective association between behavioural inhibition, and later onset of

mood and anxiety disorders in offspring of parents with anxiety disorders, major depressive disorder, and bipolar disorder. Third, given the small sample size we were unable to explore the effect that different anxiety disorders in parents had on behavioural inhibition. This is an important area for future research as one previous investigation found that fear, and avoidance in a novel situation (characteristics of behavioural inhibition) were elevated in infants of parents with social anxiety disorder but not in infants of parents with other anxiety disorders (Aktar et al., 2014). Thus, it is possible that the type of anxiety disorder in parents may influence behavioural inhibition in offspring.

3.5.5 Implications

Behavioural inhibition was nominally more common in offspring of parents with anxiety disorders regardless of the presence of a comorbid mood disorder compared to control offspring. Behavioural inhibition is associated with negative outcomes, and later anxiety disorders (Biederman et al., 1993; Hirshfeld-Becker et al., 2007). Thus, if our results are replicated in a larger sample it would suggest that children of parents with anxiety may represent a vulnerable population for anxiety disorders and unfavourable outcomes, who would benefit from preventative and intervention strategies. Previous cognitive behavioural interventions for children with behavioural inhibition who also have a parent with anxiety have proved beneficial for decreasing risk of anxiety disorders and functional impairment at follow-up (Kennedy et al., 2009; Lau et al., 2017). However, neither of these studies explored the impact a comorbid mood disorder in parents had on treatment effectiveness. If our findings hold in a larger sample then an important step for future early intervention research will be to explore the effectiveness of

cognitive behavioural interventions for inhibited children with parents with anxiety and comorbid mood disorders.

3.5.6 Conclusions

Our results provide tentative evidence that behavioural inhibition may be associated with parental diagnosis of anxiety disorders but not parental diagnosis of major depressive disorder, or bipolar disorder. If our results are replicated in a larger sample it would suggest that providing intervention to children with behavioural inhibition who also have a parent with an anxiety disorder may reduce the risk of negative outcomes, and give these children the best chance to grow up healthy.

CHAPTER 4 GENERAL DISCUSSION

4.1 Overview and Summary of Findings

Previous research has found that child temperament may be an early antecedent of a variety of psychiatric disorders (Saudino, 2005; Wichstrøm et al., 2018). Behavioural inhibition is one temperament style which has been indicated as a potential manifestation of risk for psychopathology (Dougherty et al., 2013; Dyson et al., 2011). The aim of this thesis was to explore behavioural inhibition as a risk factor for mood and anxiety disorders.

In study 1, we found that behavioural inhibition in early childhood was prospectively associated with an almost threefold increase in odds for any type of anxiety. We also found significant associations between behavioural inhibition and later diagnosis of social anxiety disorder, generalized anxiety disorder, and specific phobia. We observed the strongest relationship between behavioural inhibition and social anxiety disorder.

In study 2, we found no statistically significant differences in behavioural inhibition in any of the high-risk groups compared to controls. However, we did observe that behavioural inhibition was nominally elevated in offspring of parents with anxiety disorders, and offspring of parents with depression. When entered into the regression equation together the strength of the association between behavioral inhibition and parental anxiety disorders remained relatively the same. On the other hand, the associations between behavioural inhibition and parental mood disorders were reduced. Thus, behavioural inhibition may be specifically linked to family history of anxiety disorders.

These findings suggest that behavioural inhibition is prospectively associated with the onset of anxiety, and may be associated with family history of anxiety disorders. Taken together, our results support a strong relationship between behavioural inhibition and anxiety disorders. These findings are consistent with a large body of literature linking behavioural inhibition to risk for later anxiety (Bourdon et al., 2019; Hirshfeld-Becker et al., 2008; Rapee et al., 2009). Our results extend previous findings by quantifying the strength of the associations between anxiety disorders and behavioural inhibition, as well as providing tentative evidence that behavioural inhibition may be specifically associated with family history of anxiety disorders.

Previous research has found that behavioural inhibition is associated with familial history of depression (Olino et al., 2010; Rosenbaum et al., 2000). I sought to extend these findings by exploring behavioural inhibition in offspring of parents with major depressive disorder and offspring of parents with bipolar disorder. There was no significant association between behavioural inhibition and family history of depression or family history of bipolar disorder, although behavioural inhibition was nominally associated with parental depression. Instead, I found that behavioural inhibition in offspring of parents with mood disorders was mainly accounted for by parental anxiety. These results suggest that the previously observed relationship between behavioural inhibition and family history of depression may largely be attributable to the presence of a comorbid anxiety disorder in the parent.

There are several possible explanations for the close relationship between behavioural inhibition and anxiety disorders. First, behavioural inhibition and anxiety disorders share genetic variants (Bourdon et al., 2019), therefore the association between behavioural inhibition and anxiety may be due to a common genetic vulnerability.

Second, there are some theorists who suggest behavioural inhibition and anxiety are merely manifestations of the same construct (Rapee & Coplan, 2010). Thus, it is not surprising that behavioural inhibition and anxiety are so closely related as both may be measuring the same underlying phenomenon. However, while this theory has not been disproved there is substantial evidence which suggests behavioural inhibition and anxiety are two separate constructs. Most notable is the finding that not all children with behavioural inhibition develop anxiety, and not all individuals with anxiety were inhibited as children (Rapee & Coplan, 2010). Third, behavioural inhibition and anxiety share a number of neurofunctional features. For example, children with behavioural inhibition and individuals with anxiety both show biased attention processing of threats (Armstrong & Olatunji, 2012; Barker et al., 2015; Eysenck & Fajkowska, 2018; Henderson et al., 2015; White et al., 2017). Furthermore, hyperactivity of the amygdala in novel or threatening situations is a characteristic of both behavioural inhibition and anxiety (Clauss et al., 2015; Martin et al., 2009). Thus, neurofunctional similarities may contribute to the close relationship between behavioural inhibition and anxiety. Fourth, overprotective parenting has been found to predict stability of behavioural inhibition throughout childhood, as well as moderate the transition from inhibition to later anxiety diagnoses (Hudson et al., 2018; Johnson et al., 2016b). Overprotective parenting may be more common in children with behavioural inhibition (Kiel & Buss, 2009). Therefore, the close relationship between behavioural inhibition and anxiety may in part be attributable to overprotective parenting. Overprotective parenting is also more common in parents with mood and anxiety disorders (Gomes et al., 2015; Hudson et al., 2018). As offspring of parents with anxiety with and without a comorbid mood disorder are at

increased risk for behavioural inhibition and exposure to overprotective parenting, these children may be especially vulnerable for later anxiety diagnoses.

4.2 Future Directions

4.2.1 Implications for Future Research

The findings of this thesis have important implications for future research. It is not yet clear to what extent the relationship between behavioural inhibition and anxiety disorders is influenced by genetic factors, and to what extent this relationship is influenced by environmental factors. Future research which quantifies the role of genetic and environmental influences in the relationship between behavioural inhibition and anxiety is needed. Furthermore, behavioural inhibition is not the only temperament style which has been linked with risk for psychiatric disorders (Hirshfeld-Becker et al., 2003). Previous investigations suggest that temperament dimensions such as effortful control, surgency, and negative affect at age three and four are associated with psychiatric symptoms later in development (Wichstrøm et al., 2018). Therefore, in order to generate a better understanding of the association between temperament and later mood and anxiety disorders future research should include a broader range of temperament dimensions.

4.2.2 Implications for Early Intervention

The findings of my thesis also have implications for early interventions. Children of parents with anxiety disorders are at increased risk for behavioural inhibition. In turn, children with behavioural inhibition are more likely to develop anxiety disorders later in life. Thus, children of parents with anxiety disorders who are also inhibited may represent a vulnerable population who would benefit from early interventions. Early preventative

interventions in this population may be particularly important as previous research has established that children of parents with anxiety disorders are more likely to develop anxiety disorders themselves (Micco et al., 2009). Furthermore children with both behavioural inhibition and a parent with an anxiety disorder are more likely to develop anxiety than children with only one of these risk factors (Hudson & Dodd, 2012). Indeed 60-90% of children who have a parent with an anxiety disorder and high inhibited temperament will develop an anxiety disorder by middle childhood (Hudson & Dodd, 2012; Kennedy et al., 2009). Thus screening for behavioural inhibition in offspring of parents with anxiety disorders could facilitate allocation of at-risk children to preventative interventions.

Preliminary evidence from two studies suggests the effectiveness of prevention strategies for anxiety in children with behavioural inhibition who also have a parent with anxiety (Kennedy et al., 2009; Lau et al., 2017). These studies provided intervention to children between the ages of three and five who had high behavioural inhibition and a parent with anxiety (Kennedy et al., 2009; Lau et al., 2017). Both studies provided a parent intervention modelled after the Cool Kids Program, a cognitive-behavioural based intervention (Rapee et al., 2005). This intervention targets some of the core risk factors for anxiety disorders, including inhibited temperament, overprotective parenting, negative parenting, and parental modelling of anxiety. The intervention included psychoeducation, parent management strategies, and anxiety management skills. The focus of these sessions was to provide training on how to parent an anxious child, and how to manage the parent's own anxiety in situations with their child. One of the studies (Lau et al., 2017) also included a child component which was focused on developing social skills

during age-appropriate play. This included initiating play, communicating to maintain friends, expressing feelings, and being relaxed in social situations. In both studies at the 6-month follow-up children in the intervention condition showed significantly more gains compared to the control group; this included fewer anxiety disorders, less life interference, and reduced behavioural inhibition (Kennedy et al., 2009; Lau et al., 2017). In the one study which also included a 12-month follow-up all gains were maintained (Lau et al., 2017). Findings from past randomized controlled trials suggest that cognitive behavioural intervention for children with inhibition who also have a parent with an anxiety disorder may be beneficial at reducing risk for childhood anxiety, and life interference. However, neither of these studies included parents with major mood disorders. Thus it is unclear whether the presence of a mood disorder in the parent in addition to an anxiety disorder may interfere with intervention effectiveness. Given the high comorbidity between mood and anxiety disorders (Fava et al., 2000; Pavlova et al., 2015) it will be important for future research to explore similar interventions in inhibited children with parents who have both a mood and anxiety disorder.

4.3 Conclusions

I explored behavioural inhibition as a possible risk factor for mood and anxiety disorders. I found that behavioural inhibition in early childhood was associated with subsequent anxiety, and may be associated with parental diagnosis of anxiety disorders. These findings are novel and will aid in the design and implementation of early preventative interventions for young children at risk for anxiety disorders. Future research on behavioural inhibition in offspring of parents with mood and anxiety disorder which utilizes a larger sample size is needed to confirm the findings of the current study.

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APPENDIX A
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APPENDIX B

RESULTS SUPPLEMENT

Supplementary Material: Prospective association between behavioural inhibition and anxiety: A meta-analysis

Content:

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3, 4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6,7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	NA
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I_2) for each meta-analysis.	7-8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12,13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Supplementary Table 2.1. Demographic variables of included samples

AUTHOR	YEAR	COUNTRY	MEAN AGE BI ASSESSMENT	MEAN AGE ANXIETY ASSESSMENT	BI MEASURE	ANXIETY TYPE
BIEDERMAN	1993	USA	5.12	6.4	Observation	Any anxiety disorder, SAD, GAD, specific phobia, separation anxiety disorder
BIEDERMAN (KAGAN COHORT)	1993	USA	1.75, 4, 5.5, 7.44	11.2	Observation	Any anxiety disorder, SAD, GAD, specific phobia, separation anxiety disorder
ESSEX	2010	USA	4.5, 6.5, 8.5, 10.5, 12.5, 14.5	14.5	Observation and parent questionnaire*	Any anxiety disorder, SAD, GAD, specific phobia
HIRSHFELD-BECKER	2007	USA	4.18	9.61	Observation	Any anxiety disorder, SAD, GAD, specific phobia,

						separation anxiety disorder
HUDSON	2011 2012 2018	Australia	4.02	6.03 8.9 11.8	Observation and parent questionnaire*	Any anxiety disorder, SAD, GAD, specific phobia, separation anxiety disorder
MURIS	2010	Netherlands	6.6	8.6	Observation	Any anxiety disorder, SAD
SCHWARTZ	1999	USA	1.75, 2.58	13	Observation	Any anxiety disorder, SAD, specific phobia, separation anxiety disorder
STUMPER	2017	USA	3.55	9.16	Parent Questionnaire	Any anxiety disorder, SAD, GAD, specific phobia, separation anxiety disorder

WICHSTROM	2013	Norway	4.4	6.7	Parent Questionnaire	Symptoms
RAPEE	2014	Australia	3.8	15.4	Observation and parent questionnaire	Any anxiety disorder, SAD, GAD, specific phobia, separation anxiety disorder
MOFFITT	2007	New Zealand	3-5	18, 21, 26, 32	Observation	GAD
CASPI	2001	New Zealand	3-5	21	Observation	Any anxiety disorder
VREEKE	2013	Netherlands	4.54	5.54	Parent Questionnaire	Any anxiety disorder, SAD
VOLBRECHT	2010	USA	3.04	7.51	Observation	Symptoms
BOHLIN	2009	Sweden	20-48 months	21.3	Parent Questionnaire	Symptoms
PRIOR	2000	Australia	0.5,2 ,3.5, 5.5, 7.5, 9.5, 11.5, 12.5	13.5	Parent Questionnaire	Symptoms
CHRONIS-TUSCANO	2009	USA	1.16, 2, 4, 7	15.05	Observation and parent questionnaire*	Any anxiety disorder, SAD
EDWARDS	2010	Australia	3.95	4.95	Parent Questionnaire	Symptoms
BUSS	2011	USA	2	5.90	Observation	Symptoms
GRANT	2009	Canada	2.5	4., 6.5, 8.5, 10.5	Parent Questionnaire	Symptoms

MIAN	2011	USA	3	8.01	Parent Questionnaire	Symptoms
FRENKEL	2015	USA	1.16, 2, 4, 7	19.84	Observation and parent questionnaire	Any anxiety disorder
WHITE	2017	USA	2, 3	5.3, 7.6	Observation and parent questionnaire	Symptoms
LAHAT	2018	USA	2, 3	10.48	Observation and parent questionnaire	Symptoms
BUZZELL	2018	USA	2, 3	13.18	Observation	Symptoms
MAJDANDZIC	2018	Netherlands	1.05	2.55, 4.6	Observation	Symptoms

BI = Behavioural Inhibition, SAD = Social Anxiety Disorder, GAD = Generalized Anxiety Disorder
*main analysis based on parent report

Supplementary Table 2.2. Description of Study Quality Items and Possible Scores

Measure of study quality	Possible score
BI measure	0 = no validated, high quality instrument used 1= validated, high quality instrument 2= validated high quality instrument, and multiple measures of BI used [parent or observer] and/or multiple BI assessments
Anxiety measure	0 = no validated, high quality instrument used 1= validated, high quality questionnaire 2= Interview
Participant characteristics	0 = unrepresentative of general population/selected based on a certain characteristic 1 = Representative of general population (unselected sample)

BI=behavioural inhibition

Supplementary Table 2.3. Meta-regressions of study characteristics on the overall difference in anxiety in between children with BI and controls

SAMPLE CHARACTERISTIC	***BETA***	**CI**	**P-VALUE**
SEX	-0.004	-0.05 to 0.05	.86
MULTIPLE BI ASSESSMENTS	0.42	-0.43 to 1.27	.31
TIME BETWEEN BI AND ANXIETY	0.006	-0.05 to 0.07	.82
MEASUREMENT USED FOR BI	-0.28	-0.71 to 0.16	.20
YEAR PUBLISHED	-0.001	-0.03 to 0.03	.94
MEAN AGE BI ASSESSMENT	0.11	-0.04 to 0.26	.15
COUNTRY	-0.03	-0.28 to 0.21	.78
MEASURE OF ANXIETY	0.09	-0.54 to 0.73	.76
MEAN AGE ANXIETY	0.01	-0.05 to 0.07	.69
COMPARISION OF GROUPS	-0.15	-0.48 to 0.78	.62
STUDY QUALITY	0.32	-0.04 to 0.68	.08

BI= behavioural inhibition, CI= Confidence Interval

APPENDIX C

CODING OF BEHAVIOURAL INHIBITION VARIABLES

1. Risk Room

A. The **overall number of objects touched** by the child during the episode is recorded (score ranges from 0=no objects touched to 5= all objects touched)
B. The **time** from the start of the episode to when the child **touches each object** is recorded. The touch much be intentionally not on accident, it can include exploration rather than just playing.
C. **Fearful Affect:** Peak intensity of fearful/wary facial expression during the epoch
    0=no facial fear
    1=low intensity of facial fear, or fear is present in only on facial region
    2=definite facial expression, and fear is present in two facial regions
    3=high intensity of facial fear, all three facial regions show distinct fear expression
D. **Bodily Fear:** Peak intensity of fearful body expression during the epoch
    0=child's body never reflects fear or weariness
    1=child's body reflects low intensity of fear or weariness
    2=child's body reflects moderate intensity of fear or weariness
    3=child's body reflects high intensity of fear or weariness
E. **Vocal distress:** Peak intensity of distress vocalization during the epoch
    0=no distress vocalization
    1= mild distress vocalizations that are ambiguous in nature
    2= distress vocalizations that indicate some fear or sadness, either through the content or intonation
    3= vocalizations that indicate clearly fearful or sad overtones, either through content or intonation
F. **Proximity to parent:** The physical proximity of the child relative to the parent
    0= greater than one foot/arm's length from parent
    1= within one foot/arm's length from parent
    2 = clinging to parent
G. **References parent:** The extent the child references the parent before engaging with the object
    0= child does not comment to or glance toward the parent before engaging
    1= child looks to, or directs comment or question to parent before engaging with a toy
    2= child asks for permission or seeks reassurance from parent before engaging with a toy
H. **Tentative play:** The peak intensity of the hesitancy with which the child touches each object, or participates in each activity
    0 = no hesitancy; child readily engages in play with objects with no pauses to examine objects, AND expresses no wariness when in contact with objects
    1 = slight hesitancy; child examines object or pauses briefly (i.e., 2-5 secs) before playing with it, but then does not express wariness while in contact with the object

2 = moderate hesitancy, as indicated by any of the following: child pauses 6 or more seconds before playing with an object, or expresses wariness while in contact with the
object, or clearly avoids an object
3 = extreme hesitancy; child does not explore or touch objects at all, but may look at or point to objects

I. **Time spent playing**: The amount of time the child spends playing with the toys during the epoch. Time spent playing is only measured during phase I of the risk room
   0= child did not play with any toys during the epoch
   1= child played with toys for less than half of the epoch
   2= child played with toys for more than half of the epoch
   3 = child played with the toys for the entire epoch
J. **References Experimenter:** The extent the child references the experimenter before engaging with the object. This is only measured in phase II of the risk room
   0= child does not comment to or glance toward the experimenter before engaging
   1= child looks to, or directs comment or question to experimenter before engaging with a toy
   2= child asks for permission or seeks reassurance from experimenter before engaging with a toy

2. Stranger Approach

A. **Fearful Affect:** Peak intensity of fearful/wary facial expression during the epoch
   0=no facial fear
   1=low intensity of facial fear, or fear is present in only on facial region
   2=definite facial expression, and fear is present in two facial regions
   3=high intensity of facial fear, all three facial regions show distinct fear expression
B. **Bodily Fear:** Peak intensity of fearful body expression during the epoch
   0=child's body never reflects fear or weariness
   1=child's body reflects low intensity of fear or weariness
   2=child's body reflects moderate intensity of fear or weariness
   3=child's body reflects high intensity of fear or weariness
C. **Vocal distress:** Peak intensity of distress vocalization during the epoch
   0=no distress vocalization
   1= mild distress vocalizations that are ambiguous in nature
   2= distress vocalizations that indicate some fear or sadness, either through the content or intonation
   3= vocalizations that indicate clearly fearful or sad overtones, either through content or intonation
D. **Approach:** Peak intensity of approach behaviors
   0=no approach behaviors
   1=child makes slight movements towards stranger (i.e. leaning closer)

2=child take 1 or 2 towards the stranger
3=child takes more than 2 steps towards the stranger

E. **Avoidance:** Peak intensity of avoidance behaviors
   0=no avoidance behaviors
   1=child makes slight movements away stranger (i.e. leaning away or turns around)
   2=child take 1 or 2 steps away from the stranger
   3=child takes more than 2 steps away the stranger
F. **Gaze Aversion:** Peak intensity of gaze aversion
   0=no gaze aversion
   1= Child briefly averts gaze
   2= child glances down or away from the stranger in a deliberate attempt to avoid eye contact
   3=child makes no eye contact with the stranger at all during the epoch
G. **Verbal hesitancy:** Peak quality of the child's verbal responses to the stranger
   0=child initiates conversation with the stranger
   1= child makes neutral or eager responses to questions, either verbally or nonverbally
   2= child does not respond to questions or initiate conversation with stranger

3. Jumping Spider

A. **Fearful Affect:** Peak intensity of fearful/wary facial expression during the epoch
   0=no facial fear
   1=low intensity of facial fear, or fear is present in only on facial region
   2=definite facial expression, and fear is present in two facial regions
   3=high intensity of facial fear, all three facial regions show distinct fear expression
B. **Bodily Fear:** Peak intensity of fearful body expression during the epoch
   0=child's body never reflects fear or weariness
   1=child's body reflects low intensity of fear or weariness
   2=child's body reflects moderate intensity of fear or weariness
   3=child's body reflects high intensity of fear or weariness
C. **Vocal distress:** Peak intensity of distress vocalization during the epoch
   0=no distress vocalization
   1= mild distress vocalizations that are ambiguous in nature
   2= distress vocalizations that indicate some fear or sadness, either through the content or intonation
   3= vocalizations that indicate clearly fearful or sad overtones, either through content or intonation
D. **Gaze Aversion**: Peak intensity of gaze aversion
   0=no gaze aversion
   1= Child briefly averts gaze
   2= child glances down or away from the spider or experimenter in a deliberate attempt to avoid eye contact

3=child makes no eye contact with the spider or experimenter at all during the epoch

E. **Withdrawal:** Peak intensity of withdrawal behaviors
   0=very low withdrawal
   1=low withdrawal
   2=medium withdrawal
   3=high withdrawal

F. **Approach:** Presence of approach behaviors
   0=touches spider with no hesitation
   1=hesitates for 1 to 2 seconds before touching spider
   2= hesitates for 3 to 5 seconds before touching spider
   3=does not touch spider

G. **Startle:** Presence of startle response
   0=no startle
   1=startle

H. **Plays with spider:** Noted whether child plays with spider when given the opportunity at the end of the 4th trial
   0=no
   1=yes