Preventive interventions for youth at risk for bipolar disorder: assessing their efficacy and effects on neuroendocrine function

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A Thesis

in the Department

of

Psychology

Presented in Partial Fulfillment of the

Requirements for the Degree of

Doctor of Philosophy (Psychology, Research and Clinical Training)

at Concordia University

Montréal, Québec, Canada

August 2023

CONCORDIA UNIVERSITY

School of Graduate Studies

This is to certify that the thesis prepared

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Entitled: Preventive interventions for youth at risk for bipolar disorder: assessing their efficacy and effects on neuroendocrine function

and submitted in partial fulfillment of the requirements for the degree of

Doctor of Philosophy (Psychology)

complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

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ABSTRACT

Preventive interventions for youth at risk for bipolar disorder: assessing their efficacy and effects on neuroendocrine function

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Concordia University, 2023

Bipolar disorder (BD) is a severe and functionally impairing mental disorder that poses significant burden to family members. Offspring of parents with bipolar disorder (OBD) are at elevated risk for affective disorders. This risk is attributable to both genetic and environmental risk factors, which influence underlying stress-response systems such as the hypothalamic-pituitary-adrenal (HPA) axis. Given that OBD display dysregulated HPA functioning, which in turn prospectively predicts later affective disorders, the HPA axis might play an important role in the development of affective disorders. Programs aimed at preventing affective disorders, particularly in the OBD, have grown considerably. However, relatively few programs have targeted OBD during childhood, prior to the development of affective disorders. Furthermore, little research has examined how prevention programs impact functioning of the stress sensitive HPA axis, or how HPA axis functioning impacts individual response to such interventions. Study 1 of this dissertation was a systematic review that consisted of 33 articles from 19 studies that examined intervention programs for youth at genetic risk for BD and/or exhibiting prodromal clinical presentations (PROSPERO #443438). Preventive interventions were associated with generally positive mental health outcomes, including decreased affective and non-affective symptoms. Numerous child, parent, and environmental factors were identified to mediate program efficacy. Study 2 examined the impact of the Reducing Unwanted Stress in the Home (RUSH) prevention program on HPA axis functioning in OBD. This quasi-experimental study

examined a sample of OBD (N=26) and healthy control (N=29) children (6-11 years old) at baseline, post-, 3-, and 6-months post-intervention. Only OBD participated in the RUSH program. No group differences were observed at baseline, but OBD had lower cortisol levels than controls. Although no main effect of the intervention on cortisol levels was observed, OBD who experienced improvements in family organization and cohesion following RUSH exhibited elevated and rising cortisol levels across time. Study 3 examined whether indices of HPA functioning at baseline predict how children respond to the RUSH program. Low cortisol levels at baseline predicted improved internalizing symptoms over time in OBD, but not in controls. These studies highlight the importance of early intervention for improving mental health outcomes in the at-risk OBD. This dissertation also highlights how the HPA axis is sensitive to environmental change in families with a parent having BD, and how the neuroendocrine system may be used as an indicator of individual sensitivity to prevention.

Acknowledgments

The completion of this thesis was dependent on the support of a 'village'. First and foremost, I would like to thank my Supervisor, Dr. Mark Ellenbogen. Your support over the years helped me navigate the challenges of grad school while also learning to embrace the successes. As a result of your guidance, I gained significant competency as a researcher and a clinician, better understanding the practical implications of our research and the families we aim to help. I am also thankful to Dr. Suzanne King who provided mentorship early in my research career and helped me recognize my passion in developmental psychology. Next, I would like to thank Concordia University for allowing me to cross paths with wonderful humans who I am now fortunate to call my friends. Myr, Jules, Steph, Robbie, Sas, and Sarah, thank you for your unwavering friendship and support, and the non-stop laughter over the years. When I am 'old', reflecting on my grad school experiences, it will be the times that we spent together that I will cherish most. Elisa, Genny, Sumin, Leena, and Becky, thank you for your friendship and support over the years. Last but not least, I would like to thank my family. MYP and PYP thank you for always supporting and encouraging me to follow my dreams, especially when the dreams took me far away from home. I would not be where I am without you both. Thank you for feeding and taking care of me, even when hundreds of km separated us. TY, thank you for being my cheerleader, especially when I wanted to give up. My promise to you many years ago fueled my motivation to persevere and finish this program more than you know. Also, thank you for giving me Noah who reminds me daily why my goals and aspirations are important, and who encourages me to be the best version of myself. Thank you to my Nanny, Papa, and uncle Clive. Your steadfast belief in me over the years has made me who I am today.

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Chapter 1: General Introduction

Affective Disorders

Approximately one in five Canadians are affected by mental illness, with economic costs exceeding 50 billion dollars per year (Lim et al., 2008; Smetanin et al., 2015). Affective disorders are some of the most prevalent mental health disorders in North America, affecting anywhere from 13 to 22% of adults in the general population at a given time (Harvard Medical School, 2007; Kessler et al., 2005; Statistics Canada, 2022). Even more concerning, similar prevalence rates have been observed in adolescent populations (Merikangas et al., 2010).

Affective disorders are distinguished by changes in emotional state or affect that can significantly impair global functioning, and include bipolar disorder, major depressive disorder, among others. As per the DSM-5 (American Psychiatric Association, 2013), bipolar disorder (BD) includes both bipolar I and II disorder (BD I and BD II, respectively). BD I is characterized by manic episodes that involve a distinct period of elevated, expansive, or irritable mood, with or without a history of major depressive episode(s). Conversely, BD II consists of hypomanic episodes, which do not meet full mania clinical threshold, and a history of major depressive episode(s). Subthreshold conditions, including cyclothymic disorder and bipolar disorder-not otherwise specified, are characterized by hypomanic and depressive symptoms that do not meet clinical threshold.

BD, including subthreshold presentations, affects approximately 1 to 4.5% of the general population (Kessler et al., 2007; Ketter, 2010; Merikangas et al., 2007), and is particularly devastating due to the consequences it can impart on the affected individual and those around them. Individuals with BD are at elevated risk for comorbid mental illnesses, including anxiety disorders, ADHD, substance use disorder, as well as physical illnesses, such as obesity and

diabetes (Cassidy et al., 1999; Fagiolini et al., 2005; McIntyre et al., 2006). Of increasing concern, BD is also associated with significant morbidity and mortality (Crump et al., 2013; Ketter, 2010), with rates of suicide 30 to 40 times greater than that of the general population (Miller & Black, 2020). BD is also associated with significant functional impairment and poor quality of life, both during and between episodes (Michalak et al., 2005). Such outcomes are accompanied by substantial global illness burden, due to increased rates of disability, decreased productivity, and excess unemployment, as well as excess costs associated with direct treatment of BD and its comorbid conditions (Ketter, 2010).

Offspring of Parents with Bipolar Disorder (OBD): Developmental Outcomes

BD poses debilitating consequences to the affected individual as well as those around them, including close family members. Offspring of parents with bipolar disorder (OBD) are particularly vulnerable. Studies examining outcomes in OBD during childhood, adolescence, and adulthood have consistently reported elevated levels of psychopathology compared to offspring of parents with no mental disorder (Birmaher et al., 2009; Lapalme et al., 1997; Mesman et al., 2013; Nijjar et al., 2014; Stapp et al., 2020). Rates of affective and non-affective disorders were 31.1% and 56.8%, respectively, for OBD during adolescence and young adulthood, compared to 9.5% and 32.4% in healthy controls (Nijjar et al., 2014). OBD are 10 to 15 times more likely to develop a BD spectrum disorder compared to healthy controls (Birmaher et al., 2009; Lapalme et al., 1997). Furthermore, longitudinal assessment of OBD have found rates of bipolar spectrum disorders to increase from 3 to 13% over a 12-year follow-up, suggesting risk likely increases with age (Hillegers et al., 2005; Mesman et al., 2013). OBD are also at greater risk of developing MDD, dysthymia, anxiety disorders, behavioural disorders, ADHD, and substance use disorders (Axelson et al., 2015; Birmaher et al., 2009; Chang et al., 2001; Chang et al., 2000; Garcia-

Amador et al., 2013; Vandeleur et al., 2012). Henin et al. (2005) found developmental stage to predict the onset of psychopathology in the OBD, with depression and other anxiety disorders occurring more frequently in childhood, and BD, obsessive compulsive disorder, and substance use disorder occurring more frequently during adolescence. Concordance of psychopathology among parents has also been found to increase risk in the OBD, with mood disorder rates almost doubling when both parents are affected by BD spectrum disorder versus one (Birmaher et al., 2009; Chang et al., 2000; Vandeleur et al., 2012). Elevated risk for psychopathology in the OBD has been replicated around the globe (Garcia-Amador et al., 2013; Hillegers et al., 2005; Vandeleur et al., 2012).

In addition to elevated psychopathology, OBD also demonstrate increased risk for cognitive abnormalities, psychomotor deficits, sexual risk behaviours, lower levels of global functioning, and impairments in psychosocial functioning (Bella et al., 2011; Ellersgaard et al., 2018; McDonough-Ryan et al., 2002; Nijjar et al., 2014; Singh et al., 2007). Consistent with this, OBD are more likely to demonstrate delays in academic functioning, including weaknesses in arithmetic, spelling, and reading, and are more likely to be placed in special education classes (Henin et al., 2005; McDonough-Ryan et al., 2002).

Prevention and Early-Intervention

Adverse outcomes in the OBD are alarming, due not only to the burden they impart on the affected individual and their families, but also their cost to society at large. Recent reports have estimated lifetime economic costs of childhood mental health problems to be approximately $200 billion in Canada, with figures entering the trillions in the United States (Smith & Smith, 2010). Economic costs are associated with, but not limited to, treatment, care and support services, school programming, child welfare, the criminal justice system, and, once at working

age, loss of productivity and increased short- and long-term disability (Mental Health Commission of Canada, 2014). Given the enormity of economic costs associated with mental illness, particularly those with childhood onset, emphasis is shifting towards prevention and early intervention, especially those which target at-risk children and families. Moreover, research is accumulating to highlight the positive return on investment associated with prevention and intervention initiates (Le et al., 2021).

Prevention programs are typically aimed at reducing the prevalence and incidence rates of mental disorders, as well as altering the trajectory of illness progression. (Le et al., 2021). Three categories of prevention are typically referenced, including 1) universal prevention that targets all individuals, 2) secondary or selective prevention, which targets those at greatest risk of developing mental illness or with subthreshold clinical presentations, and 3) tertiary or indicated prevention that targets individuals already presenting with established disorders (Durlak & Wells, 1998). As OBD are at elevated risk for developing a mental disorder by way of having a parent(s) with BD and/or presenting with sub/syndromal BD, they are opportune for targeted selective and indicated prevention. Such efforts should provide a more cost-effective alternative to universal prevention.

To inform early prevention and intervention programming, it is important that etiological factors contributing to elevated risk for mental illness be elucidated. Given its complex etiology, the study of risk in the OBD has focused on different biological and psychosocial factors, following a biopsychosocial approach to understanding mental health (Borrell-Carrio et al., 2004; Engel, 1980). Such research is vital to the development of effective prevention programs (Post et al., 2020). With a better understanding of the origins of disease in the OBD, researchers

can also better predict which offspring may be at greatest risk and, thus, in greatest need of intervention.

Risk Factors in the OBD: a Biopsychosocial Framework

There is increasing interest in understanding environmental, psychological, and physiological factors that contribute to the risk for adverse outcomes in the OBD. Such factors are believed to have multi-directional impacts across systems to impact risk as well as resiliency for psychopathology and health, respectively.

With respect to genetic risk, concordance rates in studies of monozygotic and dizygotic twins are approximately 65-80% and 10-20%, respectively (Bertelsen et al., 1977; Kieseppa et al., 2004; McGuffin et al., 2003). These elevated rates of concordance result in heritability estimates at around 85% and point to the strong contribution of genetic factors in the transmission of BD across generations (McGuffin et al., 2003). Moreover, it has become increasingly known that there exists important gene-environment interplay in the development of major mental disorders (Rutter et al., 2006). As a significant proportion of children with genetic vulnerability to BD do not develop the disorder, genetic factors, while a strong predictor, are not the only risk factors at play (Brietzke et al., 2012; Duffy et al., 2010).

A substantial number of environmental factors have been associated with elevating risk in the OBD. First, the family environment of the OBD has been characterized by elevated levels of conflict and control, and lower levels of cohesion, organization, expressiveness, and adaptability (Barron et al., 2014; Chang et al., 2001; Ferreira et al., 2013; Romero et al., 2005; Shalev et al., 2019; Stapp et al., 2020). OBD exposed to greater dysfunction in the family environment have been found to evidence greater negative outcomes, including elevated internalizing and externalizing symptomatology, and increased incidence of mood or other psychiatric disorders

(Du Rocher Schudlich et al., 2008; Ferreira et al., 2013; Freed et al., 2015). Second, the parent-child relationship, incorporating parenting behaviours, has been found to be impacted by a parent having BD. Parents with BD typically provide less support, structure, and control within the home, and are more likely to use negative communications styles and to be less expressive (Iacono et al., 2018; Inoff-Germain et al., 1992; Vance et al., 2008). Furthermore, such practices have been associated with greater internalizing and externalizing symptoms, mood and anxiety disorders, and substance use symptoms (Doucette et al., 2016; Iacono et al., 2018; Meyer et al., 2006). Third, early-life adversity and trauma have also been found to increase risk in the OBD, differentiating those who go on to develop a mood disorder from those who do not (Koenders et al., 2020; Palmier-Claus et al., 2016; Schreuder et al., 2016). Finally, stressful life events, both chronic and episodic in nature, and within interpersonal and non-interpersonal domains have been elevated in the OBD (Adrian & Hammen, 1993; Ostiguy et al., 2009). Such experiences have also been posited to increase risk for affective disorders in the OBD (Petti et al., 2004).

In addition to navigating a stressful environment, OBD might lack the appropriate skills to manage such an environment. For example, OBD have been found to possess ineffective coping skills to adequately manage elevated stressors within their environment (Nijjar et al., 2014). Ineffective coping strategies may render the OBD more vulnerable to the effects of their environment, increasing their risk for developing a clinically significant mood disorder (Goodday et al., 2019). Sleep disturbances (e.g., decreased sleep and frequent awakenings at night) and disruptions in circadian rhythms have also been found to precede the development of BD (Jones, 2001; Ritter et al., 2011). Sleep disorders during childhood have been associated with a 1.6-fold increase in the development of later mood disorders, including BD (Duffy et al., 2019). In the OBD specifically, sleep patterns, including frequent awakenings during the night,

were found to predict the development of BD (Levenson et al., 2015). These findings demonstrate that the OBD are at high risk for the development of mental disorders via a complex array of biopsychosocial risk factors.

Mechanisms of Transmission

The mechanisms by which the risk factors described in the previous section increase susceptibility in the OBD are not fully known. Elevated psychosocial stress, by way of exposure to dysregulated family environments, ineffective parenting practices, and early-life adversity and stressors, are thought to impart effects 'under the skin' by altering stress-sensitive physiological systems (Doom et al., 2018; Etain et al., 2008; Hackman et al., 2013).

The hypothalamic-pituitary-adrenal (HPA) axis is a biological system that becomes activated in response to psychological and physical demand (McEwen, 1998). The HPA axis plays a pertinent role in maintaining homeostasis within the body, overseeing physiological and behavioural functions such as metabolism, immunity, and cardiovascular output, and ensuring that energy is systematically directed to various physiological functions based on priority of need (McEwen, 2007). Activation of the axis originates at the level of the hypothalamus, involving the release of corticotrophin releasing hormone from the paraventricular nucleus. Corticotrophin releasing hormone then signals the anterior pituitary to release adrenocorticotropic hormone, which finally targets the adrenal cortex through circulation, leading to the eventual release of glucocorticoids or 'cortisol' in humans (de Kloet et al., 2005; Lupien et al., 2009). With the release of cortisol into circulation, peripheral and central receptors, including glucocorticoid and mineralocorticoid receptors, become activated to initiate various physiological functions, as well as the axis' self-regulatory system. Specifically, activation of glucocorticoid receptors initiate a

negative feedback inhibition system with the primary aim of dampening activity of the HPA axis and subsequently reducing output of the axis' end-product, cortisol (Lupien et al., 2009).

It is believed that exposure to early-life stressors and associated elevations in circulating cortisol levels can significantly alter functioning of the HPA axis (Meaney & Szyf, 2005). In particular, sustained activation of the HPA axis may result in prolonged exposure to elevated cortisol levels, leading to deleterious impacts on the neurodevelopment of vulnerable populations during critical phases of development (Meaney & Szyf, 2005). In addition, continual activation of the HPA axis may result in its 'wear and tear' over time, such that the HPA axis fails to activate when confronted with a perceived threat, evidenced by patterns of cortisol hypo-responsivity in response to threat (McEwen, 2007). Evidence of elevated environmental stress being associated with dysregulated HPA axis functioning in the form of both elevated and blunted cortisol levels has accumulated (Doom et al., 2018). Changes in HPA axis functioning associated with exposure to environmental stressors are of concern, as they may increase risk for later affective disorders and other psychopathology in vulnerable populations (Ellenbogen et al., 2011).

Goals of the Dissertation

The present dissertation aimed to 1) review the literature on prevention programming for children and youth at risk for developing BD, 2) to assess if a prevention program for children at risk for BD can alter the stress-sensitive HPA system, and 3) to determine if HPA functioning can be used to predict responsivity to a prevention program. This dissertation is comprised of three manuscripts: a systematic review and two original research papers.

Paper 1 is a systematic review of the efficacy of prevention and early intervention programs for youth at risk of developing BD. At-risk status was defined as having a biological

first- or second-degree relative with BD I or II, and/or by exhibiting subthreshold symptoms for BD. Given the literature documenting the impact of environmental factors on the development of BD in at-risk populations, we were interested in examining whether interventions that aim to ameliorate such factors improve a wide-array of outcomes in youth and their family members, both in the short- and long-term. Additional aims of the study were to identify gaps within the literature and potential future directions.

Paper 2 is an original research paper that examined the impact of the Reducing Unwanted Stress in the Home (RUSH) prevention program on HPA axis functioning in a sample of OBD. In this proof-of-concept trial, OBD undergoing the prevention program were compared to age-matched controls who completed the study assessments but not the prevention. The RUSH program consisted of 12 weeks of skills-based group sessions aimed at ameliorating the family environment by promoting adaptive coping, problem solving, communication, and organization and consistency in the home. As the HPA axis is influenced by environmental stressors such as family dysfunction, we were interested in examining whether efforts to intervene at the level of the family environment induces changes in the stress response system post-intervention and up to 6-months later. Furthermore, we examined whether intervention-related changes to the family environment, specifically variables related to relationships and maintaining order in the home, were associated with corresponding changes to HPA functioning.

Finally, **Paper 3** is an original research paper that examined a novel research question within the field of prevention science. A growing number of factors have been found to impact the efficacy of prevention and intervention programs in youth at-risk of developing BD. Such variables are reviewed in Paper 1 and include parental (e.g., expressed emotion, parenting stress and negativity, family environment), offspring (e.g., therapeutic alliance, perceive conflict with

parent, mindfulness), and psychosocial factors (e.g., family psychosocial functioning), as well as neural markers (e.g., activation, functioning, and connectivity). Paper 3 attempts to examine whether pre-intervention diurnal activity of HPA axis may predict children's response to the RUSH program. Specifically, the study assesses whether baseline markers of diurnal HPA functioning predict clinical outcomes in response to the RUSH prevention program (i.e., internalizing and externalizing symptoms).

Conclusions

BD is a severe and significantly impairing mental illness, associated with substantial burden to the impacted individual and their close family members, as well as society at-large (Kessler et al., 2007). For these reasons, BD has become a public health concern, motivating increased attention to prevention and early intervention. With emphasis on intervention, increasingly efforts have been made to identify modifiable factors that increase risk for adverse outcomes or promote resiliency towards health in those at heightened risk of developing BD, such as the OBD (Stapp et al., 2020). The present dissertation aimed to understand the role of the HPA axis in prevention efforts: first as a modifiable factor that may then have the potential to reduce risk for later affective disorders, and secondly as a biomarker that identifies those individuals increasingly susceptible to positive effects of prevention. Prior to this, a review of prevention and early-intervention programs targeting youth at-risk of developing BD was conducted to examine their effectiveness in improving mental health outcomes. The research presented herein has both research and clinical utility, highlighting future directions within the field and reinforcing the need for timely prevention and early-intervention efforts.

Chapter 2: Examining efficacy and mediating factors of psychosocial preventive interventions for youth at-risk of developing bipolar disorder: a systematic review

Citation: Yong Ping, E., Alexander, C., & Ellenbogen, M.A. Examining efficacy and mediating factors of psychosocial preventive interventions for youth at-risk of developing bipolar disorder: a systematic review. (Manuscript in preparation for submission). Department of Psychology, Concordia University.

Contributions: The manuscript was conceptualized by Erin Yong Ping and Dr. Ellenbogen. Erin Yong Ping completed the initial title review, while Chesel Alexander acted as the second reviewer at the levels of abstract and full-text review, and data extraction. Dr. Ellenbogen provided supervision of the data collection and review throughout. Erin Yong Ping drafted the original manuscript, while all authors reviewed and edited the final report.

Abstract

Objectives: Bipolar disorder (BD) is a debilitating and impairing mental illness. As such, attempts to prevent and intervene in the development of the disorder have grown. The present review aimed to examine preventive interventions targeting youth at-risk for BD, focusing on mental health outcomes, mediators of change, and future directions.

Methods: A systematic review examined PsychINFO, PubMed (Medline), and SCOPUS databases to identify empirical research studies written in English or French and conducted between January 1990 to January 2023. Articles including a psychosocial prevention or intervention for youth (i.e., child, adolescent, young adult) at-risk of developing BD (i.e., at familial risk for BD and/or exhibiting early prodromal profiles of BD) were included.

Results: Thirty-three articles from 19 different studies were identified. Studies consisted of randomized controlled trials (n=9), open trials (n=5), and quasi-experimental designs (n=5). Results highlighted that at-risk youth and their caregivers stand to benefit from preventive interventions with respect to improved mental health outcomes, psychosocial functioning, sleep, and functioning of the stress response system. However, results were not always consistent nor replicated across studies. Numerous psychosocial and biological mediators were also identified.

Limitations: Several limitations were observed, including significant heterogeneity across studies making direct comparison difficult. In addition, some studies were limited by small sample sizes, relatively short follow-up periods, and weak research designs.

Conclusions: Preventive interventions have the potential to improve mental health and psychosocial outcomes in youth at-risk of developing BD. Several prevention programs require replication using larger RCT designs with extended follow-up periods. Future programs should

explore brief, web-based designs, which have the potential to help more people in need while improving cost effectiveness. (PROSPERO #443438).

Introduction

Offspring of parents with bipolar disorder (OBD) are a vulnerable population at increased risk of developing mental disorders, including bipolar disorder, major depressive disorder (MDD), anxiety disorders, and externalizing problems (Lau, Hawes, Hunt, Frankland, Roberts, & Mitchell, 2018). OBD have also been found to have poor psychosocial functioning, and overall elevated rates of morbidity and mortality, potentially linked to observed heightened levels of suicidal behaviour (Bella et al., 2011; Goldstein et al., 2011; Ranning et al., 2020). Given their elevated risk for adverse outcomes, research has increasingly focused on prevention initiatives that aim to alter developmental trajectories in OBD and mitigate risk (Post et al., 2020). It has been long emphasized that appropriately tailored and timely interventions may prevent or delay the development, or lessen the severity, of negative outcomes in OBD (Pfennig et al., 2014; Post et al., 2020; Vieta et al., 2018). Unfortunately, the body of research on preventive interventions in OBD is small, especially in comparison to empirical preventive research on externalizing problems in youth (Smedler et al., 2015).

Research on the family environment and psychosocial risk factors among OBD has been valuable in identifying potential targets for prevention and early intervention programs (Koenders et al., 2020; Palmier-Claus et al., 2016). Families affected by BD in a parent are generally more likely to report lower levels of cohesion, expressiveness, and organization and elevated levels of conflict (see reviews; Reinares et al., 2016; Stapp et al., 2020). In addition, parenting practices (i.e., insufficient control and overreactive disciplinary styles; Calam et al., 2012; Ellenbogen & Hodgins, 2004) and the parent-child relationship (e.g., perceive parental care, connection, and rejection; Doucette et al., 2016; Lau, Hawes, Hunt, Frankland, Roberts, Wright, et al., 2018; Menculini et al., 2020) have also been found to influence the development

of internalizing and externalizing symptoms, as well as affective disorders, in OBD. In a study of parents having BD and their intimate partners, environmental risk in these families appears to be worsened, rather than mitigated, by the non-affected intimate partner (Serravalle et al., 2020). In addition to having elevated rates of mental disorders, intimate partners presented with high levels of neuroticism, low levels of extraversion, frequent use of emotion-focused coping, limited social support, high marital dissatisfaction, and frequent use of verbal aggression relative to the intimate partners of a healthy control group. OBD are more likely to experience childhood adversity, including negative stressful life events (Ostiguy et al., 2009) and early trauma (Koenders et al., 2020), which are generally associated with worse clinical outcomes (Koenders et al., 2020; Menculini et al., 2020). Paired with ineffective or passive coping strategies (Kemner et al., 2015; Nijjar et al., 2014), it has been suggested that OBD possess inadequate emotional resources to cope with such elevated environmental and social stressors. Given that many risk factors in OBD and their families are modifiable in nature (Serravalle et al., 2020; Vieta et al., 2018), preventive intervention research in OBD has largely focused on improving family functioning in the home, parenting practices, and stress-coping abilities of this population.

The timing of prevention and early intervention programs for OBD and persons at risk for BD is an important consideration. The onset of bipolar disorder typically occurs during adolescence or early adulthood (Bellivier et al., 2014), with earlier onset generally associated with a worse clinical course (Van Meter et al., 2016). Along a similar vein, individuals who seek treatment for BD often endorse having experienced significant dysfunction and/or disability (e.g., educational, vocational, and social impairments) prior to their first contact with care providers (Pfennig et al., 2012). With respect to OBD, duration and timing of exposure to active BD in parents have been found to moderate the impact of parental psychopathology on clinical

outcomes. Specifically, a longer duration of exposure and exposure earlier in life have been associated with worse clinical outcomes in OBD (Doucette et al., 2016; Goodday et al., 2018). Collectively, these results suggest that prevention and early intervention programming should start early, during childhood or adolescence (Uher & Pavlova, 2018), prior to the onset of symptoms (Besenek, 2020; Van Meter et al., 2016) or during the early prodrome phase of the disorder (i.e., symptomatic period before disorder onset).

The need for early psychosocial prevention and intervention also stems from research highlighting potential adverse consequences associated with alternative forms of early intervention and treatment, namely the use of psychotropic medications. According to the clinical staging model of BD, childhood risk syndromes of non-specific psychopathology, including anxiety and sleep disorders, typically lead to depressive episodes with or without psychotic features, prior to the development of BD (Duffy et al., 2014). In OBD, the prodromal period of BD typically includes mood lability, intermittent elation or irritability, low mood, inattention, and psychosocial impairment (Miklowitz & Chang, 2008). Of concern, pharmacological treatment of anxiety, mood, and neurodevelopmental disorders have been suspected of exacerbating illness progression or accelerating the onset of mania (Baldessarini et al., 2013; Reichart & Nolen, 2004), a finding which may be amplified in juvenile populations (Baldessarini et al., 2013). As OBD are already at increased risk for mood and anxiety disorders, as well as ADHD, caution has been recommended for the use of pharmacotherapy, including antidepressant and/or stimulant medications (Goldsmith et al., 2011; Strawn et al., 2014). For these reasons, there is a growing emphasis on the development of low risk early psychosocial interventions that target this vulnerable population (Post et al., 2020).

Prevention and early intervention programs targeting OBD have typically consisted of adapted versions of disorder-specific treatment programs (Scott & Meyer, 2020). To date, two literature reviews have examined the efficacy of prevention programs, implemented prior to August 2018, for persons at risk of BD (Perich & Mitchell, 2019; Pfennig et al., 2014). Results from the reviews found some interventions, including Family Focused Therapy, Mindfulness-Based Cognitive Therapy for Children, and Multi-Family Psychoeducation Psychotherapy, to be associated with reduced symptoms, increased speed of recovery from initial mood symptoms, longer time to relapse, longer time in remission, and reduced conversion rates to BD (Perich & Mitchell, 2019; Pfennig et al., 2014). The reviews reported methodological weakness of the research, including small sample sizes and the lack of control groups. They also highlighted future directions of the field, including the need to focus on patient characteristics (e.g., symptom profile) that may affect intervention efficacy and longer follow-up to assess program's effectiveness in preventing the development of BD and other psychiatric disorders.

The present paper aimed to provide an update of the literature, systematically reviewing prevention and early intervention programs that have been developed for youth at risk of BD. Risk for BD was defined as having a first- or second-degree relative with BD I or II, and/or persons presenting with prodrome profiles, including MDD, cyclothymic disorder (CYC), or bipolar disorder-not otherwise specified (BD-NOS). Research studies incorporating psychosocial prevention/early intervention programs were reviewed to determine their efficacy in decreasing early-onset symptoms or preventing the conversion of early prodrome profiles into syndromal BD. The present paper also sought to examine how biopsychosocial factors (i.e., environmental factors, biological markers, etc.) potentially impact or mediate individual response to early intervention. Finally, the present review aimed to identify gaps within the literature that can be

used to inform future directions in the field, including the development of programming increasingly tailored to the needs or at-risk youth and their families.

Methods

A systematic literature review was conducted to examine prevention and early-intervention studies targeting youth at risk for developing BD. The protocol was registered at PROSPERO (#443438).

Search Strategy

The databases PsychINFO, PubMed (Medline), and SCOPUS were used to conduct a literature review using the following search terms "bipolar disorder, bipolar I disorder, bipolar II disorder", and "offspring, at-risk populations, high risk, risk factors, adolescent, child", and "prevention, intervention, treatment, cognitive therapy, psychotherapy". Results were limited to those studies published between January 1990 to January 2023. The references of included papers were scanned to identify additional papers not captured by the search terms.

Inclusion and Exclusion Criteria

The results were limited to those studies that 1) conducted an empirical research study, 2) examined a population at-risk for developing BD, including youth at familial risk for BD and/or exhibiting early prodromal profiles of BD, 3) included a psychosocial prevention or early intervention program, and 4) were published in English or French. Exclusion criteria were studies that examined youth already meeting diagnostic criteria for BD and/or youth above 30 years of age.

Data Screening and Extraction

Initial screening of reference titles was conducted to assess relevance to the present study. Next, abstracts were reviewed and put forth for full-text review if they were identified to meet the inclusion criteria as outlined above. Abstracts that did not provide enough information were also included at the level of full-text review. Following full-text review, studies that were confirmed to meet the inclusion criteria, but not the exclusion criteria, were included in the final literature review.

The studies deemed eligible for inclusion in the systematic review underwent data extraction. Extracted data included: authors, year of publication, country of study, study design, sample size and age, at-risk definition, prevention or early intervention program implemented and duration, type or presence of a control group, and major clinical outcomes.

The software Endnote was used at the level of title review. Titles were reviewed by the principal investigator. Next, the program DistillerSR was used at the levels of abstract and full-text review. Abstracts and full texts were reviewed by the principal investigator and a research assistant. Conflicts were resolved by a third-party reviewer (Dr. Ellenbogen). Microsoft Excel was used at the level of data extraction. Extracted variables represented discrete columns within the Excel data file.

Results

Our search yielded a total of 1383 records, of which 33 were included in the final systematic review. See Figure 1 for the Prisma Flowchart, providing a breakdown of records reviewed and removed at each stage of the review.

Study Characteristics

A total of 33 articles were found to meet all inclusion criteria and included in the final systematic review. Multiple articles examining data from the same prevention/intervention studies were included in the present review to explore potential mediators and predictors of treatment response, which was the second aim of this study. The 33 articles assessed data from a total of 19 studies. In total, 1072 youth were assessed, ranging in age from 3 to 30 years of age. Of the original 19 studies, nine used a randomized controlled trial (RCT) design (i.e., waitlist, placebo, control, or no condition), five used an open trial design, and five used a quasi-experimental control design (i.e., healthy controls or waitlist control with no randomization). The interventions used in the 19 studies were Family Psychoeducation, Family Focused Therapy (FFT), Cognitive Behaviour Therapy (CBT), Mindfulness-Based Cognitive Therapy for Children (MBCT-C), Interpersonal and Social Rhythm Therapy (IPSRT), Parent Training, Reducing Unwanted Stress in the Home (RUSH), and Family Talk Intervention (FTI) or Let's Talk about Children (LTC). The number of intervention sessions ranged from one to 24 and were conducted over a span of up to 6 months.

Preventive Interventions

Family Psychoeducation

Family psychoeducation programs were originally created to assist families in gaining knowledge and insight about serious mental illnesses affecting adult patients (McFarlane et al., 2003). They were eventually adapted to target adolescents with BD in workshop, multi-, and individual-family formats (Fristad et al., 2003). Such programs have typically focused on providing information on BD symptomatology, etiology, course, and treatment (Fristad et al., 1998). Multi-family formats have used group discussion to focus on addressing typical problems

faced by families affected by BD, including managing manic and depressive symptoms/episodes, and addressing negative family cycles (Fristad et al., 2002). Family-based psychoeducation treatments have since been adapted to target children and adolescent populations at-risk of developing BD, building social supports, fostering healthy habits, and building skills that target symptom management, emotion regulation, and communication. The program has been amended to target families in group and individual settings (Besenek, 2020; Fristad et al., 2015).

Overall, five articles from three studies were identified that targeted youth with early prodrome profiles of BD, as well as asymptomatic youth at familial risk for BD (see Table 1). All three studies used an RCT design, the gold-standard, assessing and comparing an active intervention to a waitlist control, placebo, or no intervention. The studies assessed a total of 320 children, ranging in age from 7 to 18 years. Sample sizes ranged from small (N=23) to large (N=165). While follow-up was typically limited to 3 months, one article focused on conducting a naturalistic follow-up of the original study sample, re-evaluating outcomes up to 5-years post-intervention.

Two primary interventions were identified, Psychoeducation Psychotherapy (PEP) delivered to families in individual or group settings, and a briefer psychoeducational intervention. All interventions incorporated at-risk youth and/or their families. While PEP typically intervened in youth already presenting with prodromal clinical presentations, the brief psychoeducational intervention focused on asymptomatic youth at familial risk for BD. PEP studies generally found evidence of lowered conversion rates to BD (Nadkarni & Fristad, 2010), and improvements in depressive symptoms and executive function (Fristad et al., 2015; Vesco et al., 2018). While some improvements were observed with respect to manic symptoms, they were not treatment specific, being similar in the active and control interventions (Fristad et al., 2015).

An extended follow-up study of PEP found the intervention to be associated with improved symptoms of mania, depression, executive function, and global functioning, compared to baseline, up to 5-years post-intervention (Fristad et al., 2021). However, conversion rates to BD were consistent with other longitudinal studies that assessed the natural diagnostic progression in at-risk youth (Axelson et al., 2011), suggesting that PEP did not function to lower conversion rates in the long-term (Fristad et al., 2021). Of significance, a brief psychoeducational intervention spanning one session was associated with more pronounced reductions in manic and somatic symptoms (i.e., worry about health, experience of aches and pains) across follow-up relative to at-risk children who did not receive the intervention. The brief intervention was accompanied by a booklet summarizing key points of the psychoeducational material, which may have encouraged review of material over follow-up. Overall, the results suggest that targeting youth prior to the development of psychopathology may prove worthwhile, as intervention duration can be kept to a minimum (Besenek, 2020).

Family-Focused Therapy (FFT)

FFT was initially developed for adults and children with BD, and targeted parents or spousal caregivers, siblings, and extended family members, in addition to the patient (Miklowitz & Chung, 2016). In its original form, FFT consisted of 21 sessions that spanned nine months and covered three modules: psychoeducation (i.e., signs and symptoms, etiology, strategies for relapse prevention), communication enhancement (i.e., active listening, clear communication, positive/negative feedback delivery), and problem-solving skills (i.e., identifying problems, generating potential solutions, reviewing pros/cons; Miklowitz & Chung, 2016). With respect to OBD, FFT was adapted by reducing the length of the program to four months (16 sessions) and requiring that the family member affected by BD attend with their offspring.

Eleven articles examining four studies of FFT were included in the present review (see Table 1). Studies included open trials (n=2) and RCTs (n=2) comparing the active intervention to an educational control and eventually enhanced care matched in duration. The sample sizes of the studies ranged from small (N=13) for open trial designs to large (N=127) for the multi-site RCT. Three of the four studies included follow-up to approximately 8-months post-intervention, while a larger RCT collected follow-up data 4-years post-randomization. In total, 213 youth were assessed ranging in age from 9 to 19 years. All FFT studies examined youth at familial risk for BD (i.e., first- or second-degree relative with BD) who already met diagnostic criteria for MDD, CYC, or BD-NOS.

Collectively, FFT improved affective symptoms and global functioning (Miklowitz et al., 2011), and improved the course of their presenting symptoms (e.g., rapid recovery from initial mood symptoms, increased time in remission, longer 'well' intervals; Miklowitz et al., 2013; Miklowitz, Schneck, et al., 2020). On the contrary, a large multi-site RCT failed to find differences between FFT and enhanced care in recovery times, the length of time to hypo/manic episodes, longitudinal course of symptoms, rates of conversion to BD, and symptoms of mood instability (Miklowitz, Schneck, et al., 2020; Miklowitz et al., 2022). Secondary analyses have linked FFT to improved suicidal ideation (Miklowitz, Merranko, et al., 2020) and family functioning (Weintraub et al., 2022). Furthermore, they have identified several mediating variables (e.g., expressed emotion, family functioning and conflict, and therapeutic alliance) that influence the program's efficacy in altering the course of psychopathology in youth at risk for BD (Miklowitz, Merranko, et al., 2020; Miklowitz et al., 2013; Miklowitz et al., 2021; Weintraub et al., 2022; Wong et al., 2022). FFT has since been adapted into a technology-enhanced version incorporating the use of a mobile app. The technology-enhanced version of

FFT was associated with improvements in depression symptoms and perceived parental criticism (Miklowitz et al., 2021), highlighting future directions for the field.

Finally, a number of studies have examined underlying biological mechanisms associated with participation in FFT. Relative to the control conditions, FFT has been associated with increased activation in the dorsolateral prefrontal cortex (DLPFC) and decreased activation in the amygdala and insula (Garrett et al., 2021; Garrett et al., 2015), as well as increased connectivity between the ventrolateral prefrontal cortex and anterior default mode network (Singh et al., 2021). FFT-related changes in neural activation and connectivity have predicted intervention outcomes, with increased DLPFC activation and ventrolateral prefrontal cortex and anterior default mode network connectivity associated with improved mania and depression symptoms, respectively (Garrett et al., 2015; Singh et al., 2021). However, not all effects have been specific to FFT. Decreased hippocampal and amygdala activation, and increased DLPFC activation, were associated with improved hypomania and depression symptoms, respectively, in youth exposed to both FFT and enhanced care (Garrett et al., 2021). These results suggest that FFT can elicit changes in brain activity and connectivity in regions associated with emotion regulation and cognitive control. Such changes may represent potential neural pathways by which clinical preventive interventions can impart effects on mental health.

Cognitive Behavioural Therapy (CBT)

Given impairments in affect regulation in pediatric BD populations, therapeutic treatments incorporating CBT were developed for at-risk youth. Child- and Family-Focused Cognitive Behavioral Therapy (CFF-CBT) is an integrative program that incorporates components of CBT, as well as psychoeducation and interpersonal therapy techniques (West et al., 2007). With respect to adolescents, Feeny et al. (2006) created a manualized CBT program

for the treatment of BD that built on earlier psychosocial interventions, including components of psychoeducation, medication compliance, mood monitoring, identifying and modification of unhelpful thinking patterns, identification of stressors and triggers, information about sleep hygiene, and family communication. While primarily targeting the individual, it also included some family involvement in the form of co-joint sessions with parents.

Two articles were identified that examined two prevention studies incorporating CBT principles, and interventions to improve circadian regulation, in symptomatic youth at risk for BD (see Table 1). Studies included an open trial and an RCT with small (N=14) and adequate (N=75) sample sizes, respectively. The studies assessed a total of 89 youth and young adults, 15 to 30 years of age, up to 6-years follow-up. Substantial heterogeneity existed between study designs with respect to the definition of risk (i.e., family history of BD or affective and schizoaffective disorders), type/structure of intervention, and length/duration of intervention.

An open trial of CBT (i.e., CBT-Regulation Therapy) was associated with improvements in affective symptomatology and psychosocial functioning. The intervention was found to have less effect on sleep-wake cycle disturbances, except for rise time, which was earlier post-intervention (Scott & Meyer, 2020). Chart review up to 3-years post-intervention uncovered approximately 21% of the sample had developed severe psychopathology (i.e., BD, psychotic disorder) or continued to experience mood problems without developing BD. Conversely, no intervention-specific effects were found for CBT group therapy (Leopold et al., 2020). Rather, CBT group therapy and a psychological placebo involving unstructured group meetings were both associated with improved affective symptoms and psychosocial functioning. As participants were older in age, the interventions either did not incorporate families or relied on adolescents to indicate their preference for family involvement.

Mindfulness-Based Cognitive Therapy (MBCT)

MBCT was originally developed as a prevention program to bolster recovery and prevent relapse in formerly depressed adults. The program focused on integrating cognitive therapy principles and mindfulness training (Segal et al., 2002) and was eventually adapted to target anxiety and depressive symptoms in adults with BD between episodes (Williams et al., 2008). Comorbid anxiety disorders in adults with BD has been associated with worse clinical and psychosocial outcomes, including elevated risk for suicide, highlighting its utility as a potential target for treatment (Simon et al., 2007). MBCT was eventually adapted to assist children in recognizing their thoughts, emotions, and bodily sensations, and develop mindfulness practices (MBCT-C; Lee et al., 2008). Given OBD are at elevated risk for anxiety disorders, and that pharmacological treatment of such conditions have been suspected of accelerating the onset of mania, researchers have been motivated to create effective, low-risk psychosocial interventions.

Six articles examining four studies were identified that implemented a mindfulness-based intervention to improve outcomes in OBD with an anxiety disorder or mood dysregulation (see Table 1). The four studies consisted of one open trial and three quasi-experimental designs (comparison to healthy controls or waitlist control). Sample sizes ranged from small (N=10) to adequate (N=56). A total of 115 youth were assessed ranging from 9 to 18 years of age. Three studies were limited to pre-/post-intervention designs, while one study included follow-up up to 3-months post-intervention.

Two primary interventions were identified including MBCT-C and a Mindfulness-Based Intervention (MBI) that incorporated both MBCT and Mindfulness Based Stress Reduction. Both MBCT-C and MBI were associated with improved anxiety symptoms, emotion regulation, mood lability, mindfulness, and emotion suppression (Cotton et al., 2016; Hafeman et al., 2020). An

attempt to replicate MBCT-C findings using an improved quality waitlist-controlled design was unsuccessful, however, modest success was reported with respect to improved overall illness severity (Cotton et al., 2020). Across studies, intervention-related improvements to mindfulness were associated with decreases in anxiety and depression symptoms, and improvements in emotion regulation and mood lability (Cotton et al., 2020; Cotton et al., 2016; Hafeman et al., 2020). Such results highlight the importance of mindfulness in mediating outcomes in mindfulness-based interventions.

Several articles focused on examining neural changes associated with mindfulness-based interventions. Intervention-associated decreases in activation in the left anterior cingulate cortex and bilateral insula were associated with decreased anxiety symptoms (Strawn et al., 2016). While increased functional connectivity between the posterior cingulate cortex and left DLPFC was associated with improved mood lability and emotion suppression, and to a lesser degree improved anxiety and mindfulness (Hafeman et al., 2020). Finally, studies examining the impact of MBCT-C on morphological and functional brain network organization found that intervention-related changes to path length in specific brain networks (e.g., cingulo-opercular network) predicted increased emotion regulation (Qin et al., 2021; Yang et al., 2022). In addition, right temporal pole alterations were associated with mindfulness (Yang et al., 2022). Overall, changes in neural activation, connectivity, and network organization following mindfulness-based interventions potentially represent pathways by which such interventions improve mental health outcomes in symptomatic OBD.

Interpersonal and Social Rhythm Therapy (IPSRT)

IPSRT was originally developed as a treatment program for adults with BD, which focused on developing regular daily rhythms, healthy sleep hygiene, and strategies to maintain

healthy interpersonal functioning (Goldstein et al., 2014). The program was eventually adapted to treat adolescents with BD (Hlastala et al., 2010). Given that dysregulated sleep and circadian rhythms have been found to characterize OBD (Levenson et al., 2015; Scott et al., 2022) and to represent potential risk and prodromal factors (Duffy et al., 2019), researchers have considered these factors as possible targets for early prevention and interventions. IPSRT was adapted for OBD by shortening the frequency of sessions, modifying the psychoeducation component to include parents and to directly target OBD, and adapting the interpersonal component to prioritize exploration of adolescents' emotions in response to having a parent with BD (Goldstein et al., 2014).

The review identified two articles from two studies that implemented IPSRT for youth at familial risk for BD (i.e., immediate family member diagnosed with BD; see Table 1). The studies consisted of one open trial and one randomized controlled trial with small (N=13) and adequate (N=42) sample sizes, respectively. A total of 55 youth participated in either study ranging in age from 12 to 18 years. Data collection was limited to pre-/post-intervention, lacking extended follow-up of participants.

Participation in IPSRT was not associated with changes to either mood or non-mood psychiatric symptoms (Goldstein et al., 2014; Goldstein et al., 2018). While significant changes to select sleep and circadian patterns were observed in the open trial (e.g., less weekend sleeping in and greater overall sleep continuity; Goldstein et al., 2014), such findings were not replicated in the randomized trial (Goldstein et al., 2018). While general feasibility and acceptance of the program were high, studies also reported irregular and sporadic attendance rates, potentially contributing to reduced program effectiveness (Goldstein et al., 2014; Goldstein et al., 2018).

Parent Training Prevention Programs

The Triple P-Positive Parenting Program was originally created to target high-risk children and their parents. The program aimed to intervene at the level of the parents by providing psychoeducation, teaching skills, and improving parenting confidence (Sanders, 2008). The program was eventually adapted to an internet-delivery format (Sanders et al., 2012). Web-based adaptations of the program have aimed to increase desirable behaviours and to help parents cope with undesirable ones, manage sleep routines, and provide strategies to cope with stress in the family. Specific to BD, psychoeducation about coping with the ups and downs of mood was also provided to parents (Jones et al., 2014).

Two studies were identified that examined effects of self-directed, web-based parenting interventions targeting parents with BD (see Table 1). Both studies used randomized waitlist control designs with sample sizes that ranged from adequate (N=39) to large (N=97). A total of 136 asymptomatic children between 3 to 10 years of age participated in the studies. The first study was limited by a pre-/post-intervention design and sole reliance on parent-report outcomes, including parent diagnosis. Conversely, the second study extended follow-up to 8-months post-intervention and confirmed parental diagnosis via structured clinical interview.

The first study examined the impact of Triple P-Positive Parenting Program (Jones et al., 2014), while the second study focused on Integrated Bipolar Parenting Intervention (IBPI), including sessions on self-management (e.g., managing emotions, monitoring mood, accessing support) and the Triple P-Parenting Program (Jones et al., 2017). Both programs were associated with improvements in child behaviour problems, problematic parenting practices, and parenting stress and confidence (Jones et al., 2014; Jones et al., 2017). Findings were sustained up to 8-months follow-up (Jones et al., 2017).

Reducing Unwanted Stress in the Home (RUSH)

Reducing Unwanted Stress in the Home (RUSH) was developed for families having a parent with BD (Serravalle et al., 2021). Like other family-based programs, the program sought to teach participating members about BD, as well as problem-solving and communication skills. Unlike past programs, the RUSH program also concentrated efforts on improving functioning within the caregiving environment. Parents were provided with skills to manage their children's behaviour and to improve organization and consistency within the home, and all participants were provided with effective stress-coping strategies.

The present review identified four articles from one study that examined outcomes in asymptomatic OBD who participated in the RUSH prevention program (see Table 1). The study used a quasi-experimental design, comparing asymptomatic OBD to healthy control children who completed assessments but did not participate in RUSH. The study had an adequate sample size of children (N=55) between 6 to 11 years of age. Follow-up extended to 6-months post-prevention.

The RUSH program was found to significantly reduce externalizing symptoms, but not internalizing symptoms in OBD (Serravalle et al., in preparation). Secondary analyses found RUSH to be associated with significant improvements in parental positivity (i.e., positive emotions and control) and dyadic mutuality (i.e., interactive reciprocity, cooperation, and co-responsiveness), and reductions in parental negativity (i.e., negative emotions and control). Several mediating variables, including parental negativity, parenting stress, and family functioning, were found to influence the impact of RUSH on offspring internalizing and externalizing symptoms (Resendes et al., 2023; Serravalle et al., 2021), as well as diurnal cortisol levels (Yong Ping et al., in preparation). Such markers of hypothalamic-pituitary-adrenal (HPA) axis function have been shown to predict the development of affective disorders in youth and

adult populations, highlighting a potential pathway by which preventive interventions decrease risk in OBD.

Family Talk Intervention (FTI) and Let's Talk about Children (LTC)

FTI was originally developed to assist families affected by depression in parents (Beardslee et al., 2003). The manual-based prevention included clinician-facilitated joint and individual meetings for parents and children, lasting up to 11 sessions. A brief adaptation was eventually created, LTC, that included two lecture-based group sessions for parents only (Solantaus & Toikka, 2006). While both interventions touch upon psychoeducation, family communication, child risk and resiliency factors, treatment and social support, and parenting, greater attempts are made to link material to the presenting concerns of families in FTI versus LTC.

A single study examined FTI and LTC for children of parents with BD, depression, or anxiety (see Table 1). The study used a quasi-experimental design where youth were non-randomly assigned to either FTI, LTC, or interventions as usual (i.e., control group) (Wirehag Nordh et al., 2023). A large sample of youth participated in the study (N=89), ranging in age from 8 to 17 years. Follow-up extended to 12-months after baseline.

In response to FTI and LTC, at-risk children demonstrated improved mental health across follow-up, compared to controls who demonstrated a worsening of symptoms (Wirehag Nordh et al., 2023). A change in perceived parental control was also found, such that parents in the FTI group reported enhanced parental control (i.e., more effective parenting style) compared to controls. Because the researchers did not report data by parent diagnosis, it is difficult to determine the specific impacts of FTI and LTC specifically on youth at-risk for BD.

Discussion

The present systematic review aimed to examine the efficacy of prevention and early-intervention programs developed to target youth at risk of developing BD, by way of familial risk for BD (i.e., OBD) and/or early prodrome clinical profiles. Our results highlighted substantial advancements within the field with respect to the number of programs developed to target at-risk youth. There was substantial heterogeneity among identified studies, including the definition of risk (i.e., first- or second-degree relative with BD and/or early prodrome profiles), length of intervention (i.e., single session up to 24 sessions), family member(s) targeted (i.e., at-risk youth and/or parent/caregiver), study design (i.e., RCT, quasi-experimental design, open trial, naturalistic follow-up), length of follow-up (i.e., pre/post design up to 5-year follow-up), and focus of intervention (i.e., psychoeducation, skills-development, parent training, improvement of self-regulation processes). Despite these differences, the studies collectively demonstrated that youth at risk of developing BD stand to benefit from preventive interventions, with respect to their mental health functioning and other diverse outcomes.

Broadly, preventive interventions were associated with improved mental health outcomes in youth, including reduced depression, (hypo)mania, anxiety, mood lability, suppression of negative emotions, rumination, suicidality, somatic complaints, and improved emotion regulation, and behaviour and externalizing problems (Besenek, 2020; Cotton et al., 2016; Fristad et al., 2015; Hafeman et al., 2020; Jones et al., 2014; Jones et al., 2017; Leopold et al., 2020; Miklowitz et al., 2011; Miklowitz, Merranko, et al., 2020; Serravalle et al., in preparation; Wirehag Nordh et al., 2023). Benefits also extended to parents and caregivers, including reduced parenting stress and problematic parenting, and improved perceived parental control, confidence, and positivity (Jones et al., 2014; Jones et al., 2017; Resendes et al., 2023; Serravalle et al., 2021;

Wirehag Nordh et al., 2023). Improvements were also seen in the parent-child relationship (Serravalle et al., 2021). Programs with extended follow-ups, such as FFT and family psychoeducation, demonstrated improvements in the course of psychopathology, including more rapid recovery from initial mood symptoms, increased length of remission, longer 'well' intervals, sustained decreases in hypomanic symptoms, and lower conversion rates to BD (Fristad et al., 2021; Miklowitz, Merranko, et al., 2020; Miklowitz et al., 2013; Miklowitz, Schneck, et al., 2020; Nadkarni & Fristad, 2010). Additional improvements were observed in psychosocial functioning, executive function, family functioning, and indicators of sleep quality (Goldstein et al., 2014; Miklowitz et al., 2011; Vesco et al., 2018; Weintraub et al., 2022).

Studies also reported non-significant effects. Program such as family psychoeducation, FFT, CBT, IPSRT, and RUSH failed to demonstrate program-related improvements in primary mental health outcomes (Besenek, 2020; Goldstein et al., 2014; Goldstein et al., 2018; Leopold et al., 2020; Miklowitz et al., 2022; Serravalle et al., in preparation). Similarly, some larger RCT studies were unable to demonstrate program-related effects in relation to active control groups (e.g., unstructured support group; Leopold et al., 2020) or to replicate findings reported in earlier open trial studies (Cotton et al., 2020; Miklowitz, Schneck, et al., 2020). Finally, a follow-up study of family psychoeducation was unable to demonstrate sustained mental health effects 5-years post-intervention (Fristad et al., 2021).

Collectively, research findings concerning the efficacy of preventive interventions have been mixed. As such, research has increasingly focused on identifying specific factors or 'active ingredients' that may account for positive clinical outcomes associated with early intervention (Wong et al., 2022). In the past five years, a substantial number of psychosocial variables have been found to mediate the relation between participating in an intervention and clinical

outcomes, including caregiver expressed emotion (Miklowitz et al., 2013), perceived conflict within the parent-child relationship (Miklowitz, Merranko, et al., 2020), family psychosocial functioning (Serravalle et al., in preparation; Weintraub et al., 2022; Yong Ping et al., in preparation), therapeutic alliance (Wong et al., 2022), mindfulness (Cotton et al., 2020; Cotton et al., 2016), and parenting stress and negativity (Resendes et al., 2023; Serravalle et al., 2021).

Similarly, studies have also focused on neural factors that may account for preventive intervention outcomes. FFT and MBCT-C were associated with changes in brain activation and connectivity, as well as functional and morphological network organization (Garrett et al., 2021; Garrett et al., 2015; Hafeman et al., 2020; Qin et al., 2021; Singh et al., 2021; Strawn et al., 2016; Yang et al., 2022). In turn, such changes were associated with improvements in affective and anxiety symptomatology, emotion regulation, and mindfulness (Garrett et al., 2015; Hafeman et al., 2020; Qin et al., 2021; Singh et al., 2021; Strawn et al., 2016; Yang et al., 2022). Findings, however, have not always been treatment-specific, applying to both intervention and control conditions (Garrett et al., 2021). Brain regions impacted by prevention and intervention have typically been linked to emotion regulation/processing and stress resilience (e.g., prefrontal cortex, amygdala, hippocampus, insula) and overlap with those reported in persons with BD (Olsavsky et al., 2012; Strakowski et al., 2005).

Generally, the present review highlights the far-reaching impacts of preventive interventions in youth at risk for BD and their families. As the utility of such programs becomes increasingly apparent, attempts to increase accessibility of these programs to at-risk populations will be imperative. A technology-enhanced version of FFT involving a mobile app demonstrated improvements in depression symptoms and perceived criticism, and received a generally positive reception from youth, parents, and clinicians (Miklowitz et al., 2021). These findings, paired

with positive outcomes of web-based parenting programs (Jones et al., 2014; Jones et al., 2017), demonstrate the potential ways preventive interventions can be adapted to increase accessibility to those in need. Online prevention programs are associated with reduced costs and have been thought to evoke less stigma in participating families (Jones et al., 2014). In addition, brief interventions (i.e., psychoeducation, Let's Talk about Children) that span one to two sessions, have been found to have positive results similar to their lengthier counterparts (Besenek, 2020; Wirehag Nordh et al., 2023).

Two distinct categories of studies were identified in our review, those targeting youth with early prodrome clinical profiles (e.g., Psychoeducational Psychotherapy, FFT, MBCT-C, CBT) and those examining asymptomatic youth at familial risk for BD (e.g., brief psychoeducation, parent training, IPSRT, RUSH, FTI/LTC). Generally, successful prevention programs targeting asymptomatic youth were observed to occur earlier in childhood, as young as 3 years of age, and to involve shorter interventions, in one case using only 1-2 sessions. Results from such studies provide evidence that brief, family-focused interventions hold potential to improve outcomes in at-risk populations. Future research should consider such characteristics in future program development, especially considering potential economic savings.

Despite the progress in this field, several limitations were noted. First, many of the studies were limited by small sample sizes, which likely impacted the strength of effect sizes and replicability. Second, less than half of the studies (47.4%) were able to use RCT designs, the gold-standard for examining program efficacy. Third, due to the nature of psychosocial interventions, RCTs rarely implemented double-blind research designs, where participants were blind to group assignment. Absence of a double-blind research design can introduce bias into a study, as entry into the active intervention likely raises positive expectations while entry into the

control group may elicit feelings of disappointment. Such effects increase the likelihood of detecting positive treatment effects in the active intervention. Fourth, the length of follow-up was limited to pre-/post- intervention designs in some studies, not allowing for an assessment of long-term mental health outcomes, including BD conversion rates. Fifth, youth presenting with prodrome clinical presentations at baseline often reported treatment with pharmacotherapy prior to the start of prevention program (Goldstein et al., 2018; Miklowitz et al., 2021). Treatment with medication makes it challenging to differentiate intervention effects from that of pharmacotherapy. Sixth, a limitation specific to the present review involves the heterogeneity of the studies included. Some studies examined the effects in at-risk youth of parents with affective disorders, including BD, MDD, as well as anxiety. Furthermore, results specific to the mental disorders in parents were not always made available. Finally, there was a paucity of positive replication studies for most prevention programs, suggesting that results presented herein should be interpreted with caution. Overall, continued investigation is recommended using large, multi-site, RCT designs, and extended long-term follow-up periods.

The findings presented in this paper emphasize the substantial research gains made with respect to preventing and intervening in the development of BD. Future directions in the field include continuing to identify psychosocial and biological mechanisms of change and engaging in knowledge translation to apply such information to better tailor programs to those in need. In addition, future research should aim to increase accessibility of prevention programs, such that more people can access supports during critical stages of development. Finally, more research is needed for pragmatic trials that examine the effectiveness of preventive interventions in 'real-world' settings, whereby front-line health care workers are responsible for program implementation in routine clinical settings (Singal et al., 2014).

Table 1. Prevention and intervention studies in youth at-risk for bipolar disorder. Outcomes of studies included in the systematic review.

No.	Author, Year, Country	Design/follow-up	N, Age Range	At-risk definition	Intervention	Control	Major Result
1	Nadkarni et al. (2010); USA	-Randomized controlled trial (RCT) -Groups: 1) Depressive Spectrum Disorder (DSD), 2) DSD with Transient Manic Symptoms (TMS), and 3) Bipolar Spectrum Disorder (BPSD) -Duration: 8 parent/child sessions over 8 weeks -Follow-up: baseline, 6-, 12-, and 18-months	N=165 (n= 13, DSD; n=37, DSD+TMS; n=115, BPSD) Age: 8-11 years	-Subsyndromal BD: 1) depressive spectrum disorder (DSD; major depressive disorder and/or dysthymic disorder) with transient manic symptoms (TMS) or 2) without TMS	Multi-Family Psychoeducation Psychotherapy (MF-PEP)	1-year waitlist control	-Conversion rates to BD higher for those with TMS (48.0%) compared to those without (12.5%) -Conversion rate to BD significantly lower in the immediate treatment group (16%) versus the waitlist control (60%)
2A	Fristad et al. (2015); USA	-Randomized controlled trial (RCT) -Groups: Individual Family Psychoeducational Psychotherapy (IF-PEP) + omega-3 fatty acid supplementation, 2) omega-3 + active monitoring, 3) placebo + IF-PEP, 4) placebo + active monitoring -Duration: 2 (parent/child) sessions weekly for 12 weeks -Follow-up: baseline, and 2-, 4-, 6-, 9-, and 12-weeks	N=23 (n= 5, combined; n= 7, PEP; n= 5, omega-3; n= 6, placebo) Age: 7-14 years	-Subsyndromal BD: diagnosis of BD-NOS or CYC	Individual Family Psychoeducational Psychotherapy (IF-PEP)	RCT Placebo control	-Significant improvement in depressive symptoms for those who received IF-PEP + omega-3 relative to those who received placebo conditions -Medium to large effect sizes of IF-PEP on child depression compared to active monitoring -Across all groups, manic symptoms were found to improve over time without significant treatment effects. -Combined therapy (IF-PEP + omega-3) more effective than omega-3 monotherapy, but not more effective than IF-PEP monotherapy

2B	Vesco et al. (2018); USA	-Combined two RCTs for children with depression and prodromal BD (Fristad et al., 2015) -Groups: omega-3 fatty acid supplementation + Psychoeducational Psychotherapy (PEP), 2) omega-3 monotherapy, 3) PEP monotherapy with pill placebo, 4) pill placebo -Duration: 2 (parent/child) sessions weekly for 12 weeks -Follow-up: baseline and 12 weeks	N=95 (n= 22, combined; n= 26, PEP; n= 23, omega-3; n= 24, placebo) Age: 7-14 years	-Subsyndromal BD: diagnosis of depression, BD-NOS, or CYC	Individual Family Psychoeducational Psychotherapy (IF-PEP)	RCT Placebo control	-Psychoeducational psychotherapy with omega-3 or omega-3 alone associated with significant improvements in executive function over time, including global executive composite and its two subscales: behaviour regulation (i.e., inhibition, control), and metacognition (i.e., planning, organization)
2C	Fristad et al. (2021); USA	-Naturalistic follow-up study of youth who participated in the original Omega-3 And Therapy (OATS) RCT Study -Combined groups: 1) youth with depression (OATS-D) and 2) bipolar prodromal symptoms (OATS-B) -Duration: 2 (parent/child) sessions weekly for 12 weeks -Follow-up: 2-5 years after baseline	N=38 (n=13, OATS-B; n=25, OATS-D) Age: 11-19 years	-Subsyndromal BD: diagnosis of depression, BD-NOS or CYC	Individual family Psychoeducational Psychotherapy (IF-PEP)	RCT Placebo control	-Conversion from BD-NOS/CYC to BD I/II was consistent with other longitudinal studies -Overall, participants continued to do better than baseline of the RCT for depressive and manic symptom severity, executive function, and global functioning -All symptoms were comparable to those obtained post-intervention excluding depressive symptoms, which increased significantly from the end of the RCT to follow-up (still better than baseline)

3	Besenek et al. (2020); Turkey	-Randomized controlled trial (RCT) -Groups: psychoeducational intervention (PE+) or no psychoeducational intervention (PE-) -Duration: 15-20 minutes -Follow-up: baseline, 3-, 6-, 9-months	N=60 (n=30, psychoeducation; n=30, no intervention) Age: 11-18 years	-Parents diagnosed with BD	Psychoeducational Intervention	RCT No Intervention	-Quality of life and most symptom domains did not differ between PE+ and PE- groups -Significant difference between somatic and manic symptoms across time between groups; reduction in symptom severity was greater in the PE+ group than the PE- group
4A	Miklowitz et al. (2011); USA	-One-year open trial -FFT-psychoeducation, communication, and problem-solving training -Duration: 12 sessions over 4 months -Follow-up: baseline, 4-, 8-, 12-months	N=13 Age: 9-17 years	-Parent diagnosed with bipolar I or II disorder -Subsyndromal BD: diagnosis of BD-NOS, MDD, or CYC -Youth presented with significant current affective symptoms (depression and mania)	Family-Focused Treatment for youth at High-Risk for bipolar disorder (FFT-HR)	None	-Youth demonstrated significant improvements in depression and hypo/mania symptoms across follow-up -Significant improvement found in global functioning scores -Approx. 25% conversion rate from BD-NOS to BD-I or BD-II. Comparable to rates in past studies

4B	Garrett et al. (2015); USA	-Open trial of FFT versus healthy controls -Duration: 12 sessions over 4 months -functional Magnetic Resonance Imaging (fMRI) while viewing facial expressions -Assessments: baseline and post-treatment for FFT group only. Baseline only for healthy controls.	N=24 (n=12, FFT) (n=12, healthy controls) Age: 9-17 years	-First-degree relative with bipolar I or II disorder -Youth presented with significant current affective symptoms (depression and mania)	Family Focused Therapy (FFT)	Healthy Controls	-At baseline, the OBD exhibited hypoactivation in the dorsolateral prefrontal cortex (DLPFC) and hyperactivation in the posterior cingulate cortex compared to the controls -Pre- to post-treatment brain activation increased in the DLPFC and decreased in the amygdala -Increases in the DLPFC activation were significantly correlated with improvements in mania symptoms (i.e., decreases in mania symptoms). Suggests changes in DLPFC mediate symptom change
5	Miklowitz et al. (2013); USA	-Randomized controlled trial (RCT) -Groups: 1) Family-Focused Therapy-High Risk version (FFT-HR) or 2) Educational Control (EC; 1-2 family sessions) -Duration: 12 sessions over 4 months -Follow-up: baseline, 4-, 8-, and 12-months	N=40 (n=21, FFT; n=19, EC) Age: 9-17 years	-Parent diagnosed with bipolar I or II disorder -Subsyndromal BD: diagnosis of BD-NOS, MDD, or CYC -Youth presented with significant current affective symptoms (depression and mania)	Family-Focused Therapy-High Risk version (FFT-HR)	RCT Educational control	-Relative to the EC, youth in FFT-HR demonstrated more rapid recovery from initial mood symptoms, more weeks in remission over 1 year, and a more favorable trajectory of hypomania scores (i.e., sustained decrease) -The effects of FFT-HR were more pronounced among families with high expressed emotion compared to those with low expressed emotion

6A	Miklowitz et al. (2020); USA	-Multi-site, randomized controlled trial (RCT) -Groups: Family-Focused Therapy (FFT) or Enhanced Care (EC; 6 sessions over 4 months) -Duration: 12 sessions over 4 months -Follow-up: baseline (covered 4 months prior to randomization), every 4 months for first year (4-, 8-, 12-months), and then every 6 months up to 4 years (18-, 24-, 30-, 36-, 42-, 48-months)	N=127 (n=61, FFT; n=66, EC) Age: 9-17 years	-First or second-degree relative with bipolar I or II disorder -Subsyndromal BD: diagnosis of BD-NOS or MDD -Youth presented with significant current affective symptoms (depression and mania)	Family-Focused Therapy (FFT)	RCT Enhanced Care group	-No significant difference between FFT and EC in recovery times (unlike Miklowitz et al., 2013) -FFT was associated with longer 'well' intervals from randomization to new mood episodes and from recovery to the emergence of the next mood episode compared to EC -Treatment groups did not differ on the trajectory of mood severity score during the 1-4 years of follow-up -Both groups showed significant mood symptom improvements during the treatment period and 4 months after treatment, followed by a leveling off of symptoms for the remainder of follow-up -FFT and EC groups did not differ in the rate of conversions to subsyndromal BD

6B	Miklowitz et al. (2020); USA	-Randomized controlled trial (RCT) -Groups: Family-Focused Therapy (FFT; 12 sessions) or Enhanced Care (EC; 6 sessions over 4 months) -Duration: 12 sessions over 4 months -Follow-up: baseline (covered 4 months prior to randomization), every 4 months for first year (4-, 8-, 12-months), and then every 6 months up to 4 years (18-, 24-, 30-, 36-, 42-, 48-months)	N=127 (n=61, FFT; n=66, EC) Age: 9-17 years	-First or second-degree relative with bipolar I or II disorder -Subsyndromal BD: diagnosis of BD-NOS or MDD -Youth presented with significant current affective symptoms (depression and mania)	Family-Focused Therapy (FFT)	RCT Enhanced Care group	-Youth with higher levels of suicidal ideation (SI) at baseline and who received FFT demonstrated greater reductions in SI over 1-4 years follow-up compared to those who received EC -Effects of the treatment on SI scores were mediated by changes in the youths' perceptions of family conflict; FFT-induced reductions in perceived conflict were associated with lower levels of SI in later study intervals -Youth in FFT had longer well periods characterized by no suicidal events (i.e., attempts or threatened attempts) than youth in EC
6C	Miklowitz et al. (2022); USA	-Randomized controlled trial (RCT) -Groups: Family-Focused Therapy (FFT; 12 sessions) or Enhanced Usual Care (EC; 6 sessions over 4 months) -Duration: 12 sessions over 4 months -Follow-up: baseline, every 4 months for first year (4-, 8-, 12-months), and then every 6 months up to 4 years (18-, 24-, 30-, 36-, 42-, 48-months)	N=114 (n=54, FFT; n=60, EC) Age: 9-17 years	-First or second-degree relative with bipolar I or II disorder -Subsyndromal BD: Other Specified Bipolar Disorder (OSBD) or MDD -Youth presented with significant current affective symptoms (depression and mania)	Family-Focused Therapy (FFT)	RCT Enhanced Care group	-Youth at high-risk for BD were found to have higher mood instability scores over time -No differences in mood instability over time between FFT or Enhanced Care groups

6D	Weintraub et al. (2022); USA	-Randomized controlled trial (RCT) -Groups: Family-Focused Therapy (FFT; 12 sessions) or Enhanced Care (EC; 6 sessions over 4 months) -Duration: 12 sessions over 4 months -Follow-up: baseline (covered 4 months prior to randomization), every 4 months for first year (4-, 8-, 12-months), and then every 6 months up to 4 years (18-, 24-, 30-, 36-, 42-, 48-months)	N=119 (originally N=127: n=61, FFT; n=66, EC) Age: 9-17 years	-First or second-degree relative with bipolar I or II disorder -Subsyndromal BD: diagnosis of BD-NOS or MDD -Youth presented with significant current affective symptoms (depression and mania)	Family-Focused Therapy (FFT)	RCT Enhanced Care group	-Youth assigned to FFT reported better family functioning (e.g., fewer arguments, better communication) compared to youth assigned to EC -Changes in family functioning preceded improvements in depression -Results suggest that improvements in depressive symptoms following FFT are mediated by changes in youths' perceptions of family functioning

6E	Singh et al. (2021); USA	-Randomized Controlled Trial of high-risk youth and Healthy Controls -Groups: FFT (12 sessions) or Enhanced care (6 sessions) both with medication management. And healthy controls -resting state functional Magnetic Resonance Imaging (rs-fMRI) -Duration: 12 sessions over 4 months -Assessments: baseline and 4-months (post-treatment) for FFT and EC groups. Scan at baseline only for the healthy controls	N=64 (n=34, FFT or EC; n=30, healthy controls) Age: 9-17 years	-First- or second-degree relative with bipolar I or II disorder -Subsyndromal BD: diagnosis of BD-NOS or MDD -Youth presented with significant current affective symptoms (depression and mania)	Family-Focused Therapy for High-Risk youth (FFT-HR)	RCT Enhanced Care group and Healthy controls	-Symptomatic youth with family history of BD had greater intrinsic connectivity between the ventrolateral prefrontal cortex (VLPFC) and anterior default mod network (aDMN) than did healthy controls -Across follow-up, high-risk youth assigned to FFT demonstrated increased connectivity from pre- to post-treatment in VLPFC-aDMN connectivity, versus the EC group who showed no significant change over time -Enhanced aDMN connectivity inversely correlated with improvements in depression severity in the FFT group but not the EC group

6F	Garrett et al. (2021); USA	-Randomized Controlled Trial of FFT -Groups: FFT or Enhanced Care (EC), both with medication management -functional Magnetic Resonance Imaging (fMRI) while viewing facial expressions -Duration: 12 sessions over 4 months -Assessments: baseline and post-treatment (FFT or EC)	N=40 (n=20, FFT) (n=20, EC) Age: 9-17 years	-First- or second-degree relative with bipolar I or II disorder -Subsyndromal BD: diagnosis of BD-NOS or MDD -Youth presented with significant current affective symptoms (depression and mania)	Family Focused Therapy for High-Risk youth (FFT-HR)	RCT Enhanced Care group	-Youth in FFT showed increasing activation in the dorsolateral prefrontal cortex (DLPFC) and decreasing activation in the insula from pre-to post-treatment -EC group showed decreasing DLPFC and no change in insula activation -Across both groups, decreasing activation in the hippocampus and amygdala from pre- to post-treatment were correlated with improved hypomania symptoms -Across both groups, increasing activation in the DLPFC from pre- to post-treatment were correlated with improved depression symptoms
7A	Miklowitz et al. (2021); USA	-Open trial of FFT -Duration: 12 sessions over 4 months -Follow-up: baseline, 9- (mid treatment), 18- (post-treatment), and 27-weeks (follow-up)	N=22 (adolescents) N=34 (parents) Age: 13-19 years	-Parent with major depressive disorder of bipolar disorder I or II -Youth with a history of mood instability and impairment -Youth presented with significant current affective symptoms (depression and mania) -Parent(s) high in perceived criticism	Technology-enhanced Family-Focused Therapy (FFT)	None	-Mobile-enhanced version of FFT associated with considerable variability in engagement in adolescents and parents, and across the tasks -Adolescents demonstrated significant reductions in depression symptoms -Adolescents reported reductions in amount of perceived criticism from parents, and feeling less distressed by criticism -Reductions in perceived criticism were correlated with improvements in depression symptoms

7B	Wong et al. (2022); USA	-Open trial of FFT -Groups: Family-Focused Therapy (FFT; 12 sessions) -Duration: 12 sessions over 4 months -Follow-up: Baseline and 18-weeks (post-treatment)	N=17 (adolescents) N=22 (parents) Age: 13-19 years	-Parent with major depressive disorder of bipolar disorder I or II -Youth with a history of mood instability and impairment -Youth presented with significant current affective symptoms (depression and mania) -Parent(s) high in perceived criticism	Technology-enhanced Family-Focused Therapy (FFT)	None	-Parents had significantly higher levels of engagement and emotional connection with therapists than their offspring -Adolescents' therapeutic engagement scores were significantly correlated with reductions in depression scores over 18 weeks
8	Leopold et al. (2020); Germany	-Randomized controlled trial -Groups: 1) cognitive-behavioral group therapy (BEsT (be)for(e) Bipolar ©) or 2) psychological placebo (unstructured group meetings) -Duration: 14 weekly sessions -Follow-up: baseline and 7- (safety visit), 14- (post-treatment), 24-, 52-weeks, 78-weeks	N=75 (n=38, group CBT) (n=37, psychological placebo) Age: 15-30 years	-First- or second-degree relative with affective and/or schizoaffective disorders -Subsyndromal BD: subthreshold mania, subthreshold depression with cyclothymic features, cyclothymic features -Youth presented with reduction in psychosocial functioning	Cognitive-Behavioral Group Therapy	RCT Psychological Placebo group	-Depression symptoms and psychosocial functioning significantly improved over follow-up for all participants, no treatment-specific effects observed over time -Severity of mania symptoms for the whole sample decreased significantly from baseline to 24 weeks post-randomization

9	Scott et al. (2021); UK	-Open trial of CBT-REG -Case series -Duration: 24 weekly sessions -Follow-up: pre-treatment, post-treatment (approx. 24 weeks later), 2-3 year post-treatment chart review	N=14 Age: 16-26 years	-Mood-related problems in the past 2 years -Currently help-seeking -At-risk of BD (i.e., family history of BD or MDD, early expressions of psychopathology, or subthreshold conditions)	Cognitive Behavioral Therapy - Regulation Model (CBT-REG)	None	-Youth demonstrated large decreases in distressing symptoms, as well as depression, activation, and rumination over the course of the study -Changes in social and behavioural regulation and time of awakening were also observed -Less evidence for the overall effect of CBT-REG on sleep-wake cycle disturbances -Promising levels of engagement -Only half of the youth selected to engage in family sessions - many at-risk youth were already living independently
10A	Cotton et al. (2016); USA	-Open trial of MBCT-C -Two age groups: younger group (9-12 years) and older group (13-16 years) -Duration: 12 weekly sessions -Follow-up: baseline, 6- and 12-weeks	N=10 Age: 9-17 years	-At least one parent with bipolar I disorder -Diagnosed with an anxiety disorder (i.e., generalized anxiety disorder, separation anxiety disorder, panic disorder, and/or social phobia/social anxiety disorder) -Youth presented with current symptoms of anxiety	Mindfulness-Based Cognitive Therapy for Children (MBCT-C)	None	-Anxiety significantly decreased following the intervention, while emotion regulation significantly increased -After the intervention, elevated mindfulness was associated with lower youth anxiety -High levels of feasibility, acceptability, and usefulness of the intervention reported by parents/caregivers and children

10B	Strawn et al. (2016); USA	-Open trial of MBCT-C on neural function -functional Magnetic Resonance Imaging (fMRI) while performing the continuous processing task -Duration: 12 weekly sessions -Assessments: pre- and post-intervention	N=9 Age: 9-16 years	-Family history of bipolar disorder -Met diagnostic criteria for an anxiety disorder (i.e., generalized anxiety disorder, social anxiety disorder, and/or separation anxiety disorder)	Mindfulness-Based Cognitive Therapy for Children (MBCT-C) 12 weeks	None	-MBCT-C was associated with increases in activation of the bilateral insula, lentiform nucleus, and thalamus, as well as the left anterior cingulate, while completing a cognitive processing task -Decreased functional activation of the left anterior cingulate cortex and bilateral insula predicted treatment-associated decreases in anxiety symptoms -Baseline activation in the left anterior cingulate and right anterior insula predicted treatment-related changes in anxiety symptoms
11	Cotton et al. (2020); USA	-Quasi experimental design -Groups: MBCT-C only and waitlist control (education materials 12 weeks prior to MBCT-C) -Duration: 12 weekly sessions -Follow-up (waitlist): baseline, 4-, 8-, and 12-weeks. Follow-up (treatment): weekly up to 12 weeks	N=24 (n=5, MBCT-C only; n=19, waitlist control subset) Age: 9-18 years	-At least one biological parent with bipolar I disorder -Diagnosed with an anxiety disorder (i.e., generalized anxiety disorder, separation anxiety disorder, social anxiety disorder, or panic disorder) -Youth presented with current symptoms of anxiety	Mindfulness-Based Cognitive Therapy for Children (MBCT-C)	Waitlist Control	-Significant improvements in overall clinical severity were observed when youth were completing the MBCT-C program compared to the waitlist control period -No significant change in anxiety, emotion regulation or mindfulness; past findings not replicated -Increase in mindfulness during MBCT-C was associated with improvements in anxiety and emotion regulation, but not during the waitlist period

12	Hafeman et al. (2020); USA	-Quasi experimental design -Groups: Youth with family history of BD treated with Mindfulness Based Intervention (MBI) and healthy controls -functional Magnetic Resonance Imaging (fMRI) to obtain resting-state functional connectivity (rsFC) pre- and post-treatment -Duration: 8 weekly sessions -Follow-up (MBI): baseline, pre-treatment, post-treatment, 3-months post-treatment. Follow-up (controls): pre- and post-treatment scans	N=35 (n=20, youth with family history of BD and mood lability; n=15, healthy controls) Age: 10-14 years	-First-degree (parent or sibling) family history of BD -Elevated mood lability in youth	Mindfulness-Based Intervention (MBI; based on Mindfulness Based Cognitive Therapy and Mindfulness Based Stress Reduction)	Healthy Controls	-Mindfulness-based intervention associated with increased rsFC between posterior cingulate cortex (PCC) and left dorsolateral prefrontal cortex (dlPFC) that was not replicated in controls -PCC-DLPFC rsFC increases predicted less mood lability and less emotion suppression, less anxiety (trend), and greater mindfulness (trend) at follow-up -MBI was associated with improvements in mood lability, anxiety, and mindfulness, and a decrease in emotion suppression -Later increases in mindfulness (between post-treatment and 3-month follow-up) correlated with improvements in mood lability, depression, anxiety, and emotion suppression)

13A	Qin et al. (2021); USA	-Open trial of MBCT-C on network-level functional topological changes -Resting state functional Magnetic Resonance Imaging (rs fMRI) scans before and after treatment -Duration: 12 weekly sessions -Follow-up: Pre- and post-treatment	N=10 Age: 13-17 years	-Biological parent with Bipolar I disorder -Youth with current symptoms of mood dysregulation (i.e., depression, mania, or emotion dysregulation)	Mindfulness-Based Cognitive Therapy for Children (MBCT-C)	None	-Following MBCT-C, youth demonstrated higher network efficiency and decreased characteristic path length within the cingulo-opercular network (CON) and fronto-parietal network (FPN) (i.e., enhanced functional integration of the dual-network) -Enhanced functional connectivity strength of frontal and limbic areas identified within the default mode network (DMN) and CON following MBCT-C -Change in path length within the CON was significantly related to changes in emotion regulation (associated with an improvement in emotion regulation)

13B	Yang et al. (2022); USA	-Quasi experimental design examining morphological brain network organization -Groups: mood dysregulated OBD treated with MBCT-C and healthy controls -Resting state functional Magnetic Resonance Imaging (rs fMRI) -Duration: 12 weekly sessions -Follow-up: pre- and post-treatment	N=25 (n=10, mood dysregulated; n=15, healthy controls) Age: 10-17 years	-Biological parent with bipolar I disorder -Youth with current symptoms of mood dysregulation (i.e., depression, mania, or emotion dysregulation)	Mindfulness-Based Cognitive Therapy for Children (MBCT-C)	Healthy Controls	-Mood dysregulated youth demonstrated randomized brain network organization at baseline compared to healthy controls (i.e., increased global efficiency, decreased path length, and abnormal nodal properties) -MBCT-C therapy associated with significant alterations (i.e., reduced global efficiency and increased path length), suggesting shift towards healthy controls -Baseline right temporal pole alterations predicted a significant change in mindfulness after MBCT-C -Changes in path length following MBCT-C were correlated with improved emotion regulation scores
14	Goldstein et al. (2014); USA	-Open trial of IPSRT -Duration: 12 sessions over 6 months -Follow-up: baseline, 3-, and 6-months	N=13 Age: 12-18 years	-Biological parent and/or sibling with Bipolar I or II disorder	Interpersonal and Social Rhythm Therapy (IPSRT)	None	-Significant change in select sleep and circadian patterns over the course of treatment, including less oversleeping on weekends/less sleep time on weekend nights, shift toward earlier wake times on weekend mornings, later bedtimes on school nights -Minimal improvements in overall psychiatric symptoms/illness with IPSRT -Treatment attendance was sporadic (64%) attributable to parental BD illness severity

15	Goldstein et al. (2018); USA	-Randomized trial to IPSRT or control -Groups: IPSRT plus data-informed referral (IPSRT + DIR) or DIR-alone -Duration: 8 sessions over 6 months -Follow-up: baseline, 3-, and 6-months -Self/parent report measures every 6 weeks (i.e., baseline, 1.5-, 3-, 4.5-, and 6-months)	N=42 (n=21 IPSRT+DIR; n=21 DIR-alone) Age: 12-18 years	-Parent with Bipolar I or II disorder	Interpersonal and Social Rhythm Therapy (IPSRT)	Data-informed referral group	-Irregular attendance for IPSRT; IPSRT+DIR youth attended half of the scheduled sessions, suggesting challenges with treatment engagement and retention -No differences were found in mood and non-mood psychiatric symptoms, nor symptoms of sleep between the two groups -Youth in the DIR-alone group tended to have higher baseline scores on most outcomes -Trend toward youth in the IPSRT+DIR group having fewer subthreshold hypo/manic symptoms versus DIR-alone -IPSRT+DIR group demonstrated better sleep continuity at follow-up than baseline
16	Jones et al. (2014); UK	-Randomized controlled trial of a web-based parenting intervention based on Triple P-Positive Parenting Programme -Groups: Triple P-Positive Parenting Programme or a waitlist control -Duration: 10 weekly sessions -Follow-up: baseline and 10-weeks	N=39 (n=19, active treatment; n=20, waitlist control subset) Age: 4-10 years	-Parents with bipolar disorder (self-report)	Web-based parenting intervention based on Triple P-Positive Parenting Programme	Waitlist control	-The parenting intervention was associated with greater improvements in child behaviour problems compared to the waitlist control -Similarly, the parenting intervention was associated with significant improvement in problematic perceived parenting compared to controls

17	Jones et al. (2017); UK	-Randomized controlled trial of Integrated Bipolar Parenting Intervention (IBPI) -Groups: IBPI plus treatment as usual, or waitlist control -Duration: 16 weekly sessions -Follow-up: baseline, 16-(end of intervention), 24-, 36-, and 48-weeks	N=97 (n=47, active treatment; n=50, waitlist control subset) Age: 3-10 years	-Parent with bipolar disorder	Integrated Bipolar Parenting Intervention (IBPI) + Treatment as Usual	Waitlist control	-Retention rate was 90%. 75% accessed the bipolar self-help modules. 53% accessed the Triple P module -IBPI participants improved relative to the waitlist control -Child behaviour problems improved significantly during access to IBPI and were sustained throughout follow-up -Parenting stress and confidence improved significantly during the intervention and were sustained throughout follow-up -Dysfunctional parenting also improved during IBPI but only marginally
18A	Serravalle et al. (in prep); Canada	-Quasi-experimental trial of Reducing Unwanted Stress in the Home (RUSH) intervention versus no treatment in healthy controls -Groups: offspring of parents with bipolar disorder (OBD)and healthy controls -Duration: 12 weekly sessions -Follow-up: baseline, 3-, 6-, 9-months	N=55 (n=26 OBD; n=29 controls) Age: 6-11 years	-Biological offspring of parents with bipolar I or II disorder	Reducing Unwanted Stress in the Home (RUSH)	Healthy Controls	-RUSH was associated with reduced externalizing behaviors and improved organization in the family environment directly following treatment. Gains in family organization persisted up to 6-months post-prevention. Changes in family conflict also appeared 6-months post-prevention -RUSH-associated changes in organization were related to decreases in externalizing behaviours in the OBD up to 6-months post-prevention

18B	Serravalle et al. (2021); Canada	-Quasi-experimental trial of Reducing Unwanted Stress in the Home (RUSH) intervention versus no treatment in healthy controls -Groups: offspring of parents with bipolar disorder (OBD)and healthy controls -Duration: 12 weekly sessions -Follow-up: baseline, 3-, 6-, 9-months	N=55 (n=26 OBD; n=29 healthy controls) Age: 6-11 years	-Biological offspring of parents with bipolar I or II disorder	Reducing Unwanted Stress in the Home (RUSH)	Healthy Controls	-RUSH was associated with reduced parental negativity and enhance parent positivity and dyadic mutuality (i.e., cooperation) directly following the intervention and at 6-months follow-up -Improvements in parental negativity following participation in RUSH associated with decreased levels of child internalizing symptoms in the OBD
18C	Resendes et al. (2021); Canada	-Quasi-experimental trial of Reducing Unwanted Stress in the Home (RUSH) intervention versus no treatment in healthy controls -Groups: offspring of parents with bipolar disorder (OBD)and healthy controls -Duration: 12 weekly sessions -Follow-up: baseline, 3-, 6-, 9-months	N=53 (n=25, OBD; n=28, healthy controls) Age: 6-11 years	-Biological offspring of parents with bipolar I or II disorder	Reducing Unwanted Stress in the Home (RUSH)	Healthy Controls	-Parents with BD reported less perceived difficulty caring for their child and less overall interpersonal and total stress immediately following RUSH and up to 6-months post-intervention compared to controls -RUSH-induced reductions to parenting stress, mediated the relationship between participating in RUSH and OBD internalizing and externalizing problems at follow-up

18C	Yong Ping et al. (in prep); Canada	-Quasi-experimental trial of Reducing Unwanted Stress in the Home (RUSH) intervention versus no treatment in healthy controls -Groups: offspring of parents with bipolar disorder (OBD) and healthy controls -Duration: 12 weekly sessions -Follow-up: baseline, 3-, 6-, 9-months	N=55 (n=26, OBD; n=29, healthy controls) Age: 6-11 years	-Biological offspring of parents with bipolar I or II disorder	Reducing Unwanted Stress in the Home (RUSH) 12 weeks	Healthy Controls	-No significant differences observed between the OBD and healthy controls on indices of HPA axis functioning at baseline or across time -OBD who demonstrated improvements in family organization or cohesion in response to RUSH exhibited significant changes in HPA axis functioning (i.e., cortisol response to awakening, daily total output, diurnal slope) across time
19	Wirehag North et al. (2022); Sweden	-Quasi-experimental trial of Family Talk Intervention (FTI), Let's Talk about Children (LTC) -Groups: FTI, LTC, or Intervention as usual (IAU) -Duration: 6-8 sessions (FTI), or 1-2 sessions (LTC) -Follow-up: baseline, 6-, and 12-months	N=89 (n=35, FTI; n=16, LTC; n=38, IAU) Age: 8-17 years	-Offspring of parents with depression, anxiety, or bipolar disorder	Family Talk Intervention (FTI) and Let's Talk about Children (LTC)	Intervention as usual	-Parents in FTI and LTC reported more favorable outcomes in terms of preventing the increase in child mental health problems up to 12-months follow-up, compared to the IAU group -FTI and LTC were associated with improved/enhanced perceived parental control compared to IAU (i.e., strengthened belief that they can handle their child's difficult behaviours). Evidence in LTC not as strong as FTI -No significant differences between FTI and LTC

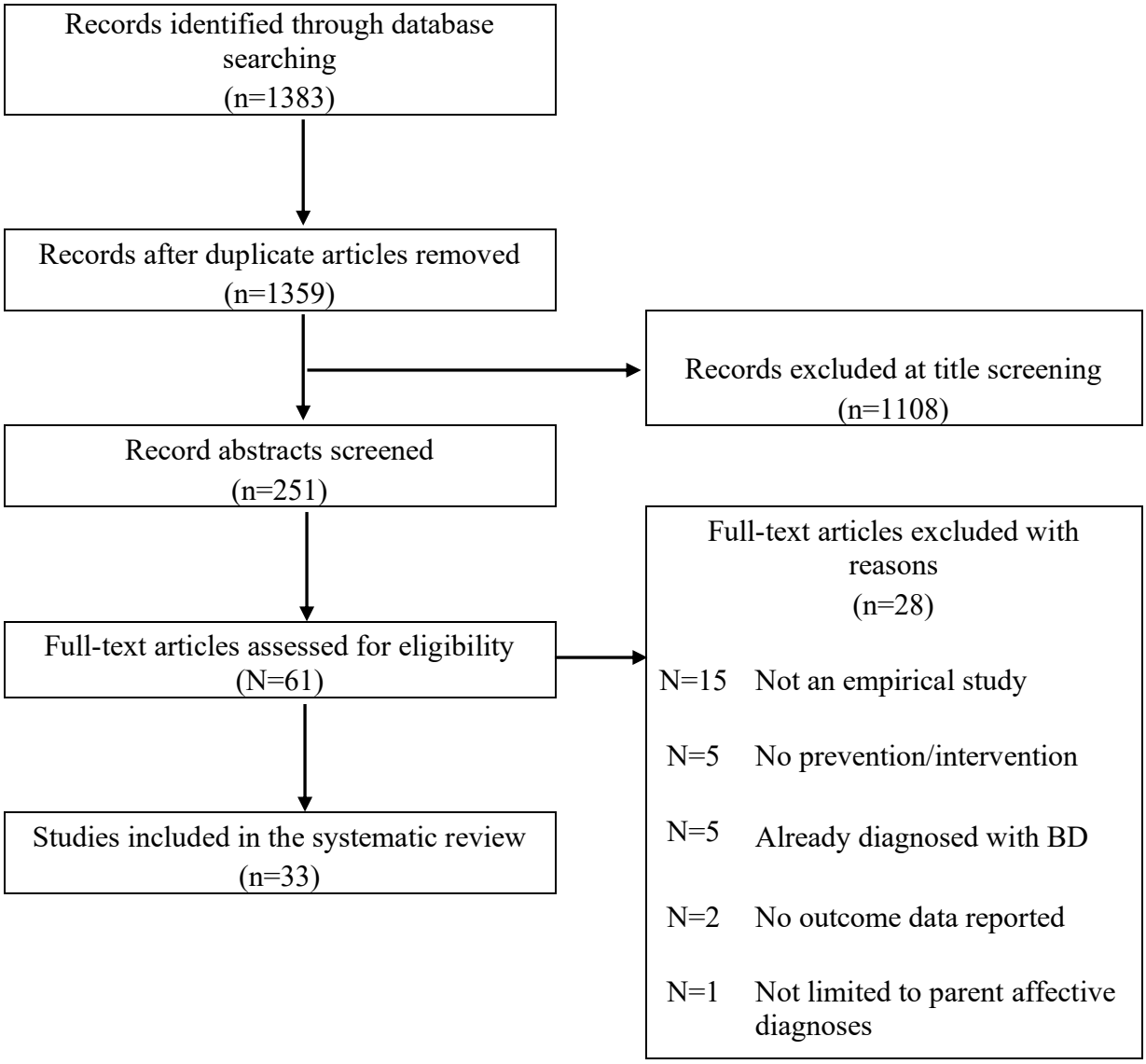

Figure 1. Prisma Flowchart

Transition Paragraph 1

Preventive interventions directed toward youth at risk of developing BD and their families have been associated with, for the most part, positive mental health and psychosocial outcomes. A substantial number of mediating variables, pertaining directly to the at-risk youth (e.g., level of mindfulness) and their environment (e.g., perceived conflict with parent, family functioning, parental stress and negativity) have been found to explain, in part, how prevention programs lead to improved youth outcomes. Furthermore, prevention-related changes to various biological markers, such as brain activation and connectivity in regions associated with emotion processing and regulation, have been found to influence individuals' response to these programs. With increasing evidence to illustrate the impact of preventive interventions on mental health functioning, the second study of this dissertation aimed to examine one putative biological mechanism of such change. Reducing Unwanted Stress in the Home (RUSH), a family-based prevention program, targeted offspring of parents with bipolar disorder during childhood, prior to the onset of symptoms of an affective disorder. Study 2 aimed to examine the impact of the RUSH program on hypothalamic-pituitary-adrenal (HPA) axis function. Specifically, the study sought to first examine whether participation in the program altered HPA axis functioning in the OBD and second to examine whether such changes were mediated by improvements to the family environment. Results from this study are particularly valuable, as they stand to identify one putative underlying mechanism by which preventive interventions exert their effects and, in turn, potentially lower risk for later psychopathology.

Chapter 3: Hypothalamic-pituitary-adrenal axis function in the offspring of parents with bipolar disorder following the Reducing Unwanted Stress in the Home (RUSH) prevention program

Citation: Yong Ping, E., Herriot, H., Iacono, V., Serravalle, L., & Ellenbogen, M.A. Hypothalamic-pituitary-adrenal axis function in the offspring of parents with bipolar disorder following the Reducing Unwanted Stress in the Home (RUSH) prevention program. (Revised and resubmitted to Psychoneuroendocrinology).

Contributions: This manuscript was conducted using data previously collected for the Reducing Unwanted Stress in the Home (RUSH) prevention study, which was initiated and organized by Drs. Ellenbogen and Iacono, and Lisa Serravalle. In collaboration with Dr. Ellenbogen, Erin Yong Ping conceptualized the research question and the selection of the necessary data to answer the research question. Dr. Herriot provided support in completing and interpreting the statistical analyses. Under the supervision of Dr. Ellenbogen, Erin Yong Ping interpreted the data and drafted the manuscript. All authors participated in reviewing and editing the manuscript.

Abstract

Background: The home environment of offspring of parents with bipolar disorder (OBD) has been characterized by high levels of stress and disorganization, which may impact development of the hypothalamic-pituitary-adrenal (HPA) axis and their subsequent risk for affective disorders. The present study examined the effects of a family-based preventative intervention on the OBD's HPA axis functioning and whether intervention-related changes in the home environment might have driven change in the HPA axis.

Methods: Fifty-five children (6 to 11 years) from families affected by BD in a parent (n=26) and healthy control families (n=29) participated in the study. Only those families with a parent having BD participated in the preventative intervention. Both groups completed assessments at baseline, post-prevention, 3-, and 6-months post-prevention. At each assessment, family organization, control, cohesion, conflict, and expressiveness, in addition to childhood internalizing problems, were measured, and offspring saliva samples were collected across two consecutive days.

Results: Hierarchical Linear Modelling found no significant differences in HPA axis functioning between groups at baseline or across time. Improvements in family organization, however, were associated with elevations in participants' cortisol awakening response (CAR; $p = .004$) and total daily output ($p = .023$), and a steepening of their diurnal slope ($p = .003$) across time. Similar findings were obtained for family cohesion with respect to CAR ($p < .001$) and, to a lesser degree, diurnal slope ($p = .064$).

Discussion: HPA axis functioning did not differ between the OBD and healthy controls at baseline or in response to the preventative intervention. However, intervention-related

improvements in family organization and, to a lesser degree, cohesion, were associated with adaptive changes in HPA functioning over time.

Introduction

Bipolar disorder (BD) affects approximately 1-3% of the global population (Merikangas et al., 2011) and is associated with psychosocial impairment, comorbid mental health disorders, and morbidity and mortality (Crump et al., 2013). Among families having a parent with BD, the disorder and its concomitant problems may also negatively impact the development of their children. Offspring of parents with BD (OBD) are at elevated risk for psychiatric disorders, including BD, major depressive disorder, and anxiety disorders (Birmaher et al., 2009; Duffy et al., 2019; Nijjar et al., 2014). While high heritability estimates indicate a strong genetic component in the transmission of risk from parent to offspring (McGuffin et al., 2003), parent behaviors and family functioning may also elevate risk for adverse outcomes in the OBD (Ellenbogen & Hodgins, 2004).

The family environment of OBD has been characterized by lower levels of cohesion, organization, expressiveness of emotions, and elevated conflict and non-optimal parenting practices compared to controls (see review Stapp et al., 2020). Parents with BD and their partners also describe the home environment as having elevated dependent stressful life events, high marital distress, and smaller and inadequate social support networks relative to parents having no mental disorder (Serravalle et al., 2020). OBD exposed to these parenting and family risk factors are at increased risk for developing mental disorders, relative to OBD and controls with few family risk factors (Iacono et al., 2018; Stapp et al., 2020). Thus, OBD may be subject to greater stress and disruptions in family functioning in childhood, subsequently increasing their risk for later development of psychopathology.

Exposure to poor family functioning may increase risk for offspring psychopathology in part by disrupting neuroendocrine function of the hypothalamic-pituitary-adrenal (HPA) axis

(Lupien et al., 2009). The HPA axis plays an important role in regulating one's physiological response to elevated psychological and physical demand (McEwen, 1998). Exposure to environmental stressors may place demands on the HPA axis, leading to its 'wear and tear' and eventual dysregulation, evident through altered circulating cortisol levels (McEwen, 1998). Children exposed to stressful home environments in the form of elevated chaos and maltreatment, have been found to display dysregulated HPA axis functioning via blunted and elevated diurnal cortisol profiles, and decreased morning cortisol levels (Doom et al., 2013; Doom et al., 2018; Lumeng et al., 2014). Ellenbogen and Hodgins (2009) found that OBD exposed to low levels of structure (organization and consistency) in the home during middle childhood displayed an elevated cortisol response following awakening (CAR) and higher cortisol reactivity to a psychosocial stressor in adolescence compared to controls. Overall, the effects of the family environment on HPA axis functioning may represent a pathway by which environmental stress is transmitted 'under the skin', subsequently increasing offspring's vulnerability for later psychopathology (Miller et al., 2011).

Evidence of dysregulated HPA axis functioning in individuals with affective disorders has accumulated (Ellenbogen et al., 2019; Lopez-Duran et al., 2009), with elevated cortisol levels largely predictive of depression in children, adolescents, and adults (Kennis et al., 2020; Lopez-Duran et al., 2009). Similar, albeit less severe, dysregulation of the HPA axis has been reported in populations at-risk for the development of an affective disorder, such as the OBD. Adolescent OBD have been found to exhibit elevated CAR and daytime cortisol levels compared to healthy, age-matched controls (Ellenbogen et al., 2004; Ellenbogen et al., 2006), and such patterns have been found to persist into adulthood (Ellenbogen et al., 2010; Ostiguy et al., 2011). Indeed, elevated cortisol levels in adolescence predicted the development of an affective disorder

among the OBD in a prospective follow-up study (Ellenbogen et al., 2011), and similar findings were reported among offspring of mothers with depression (Halligan et al., 2007). Taken together, elevated cortisol levels in at-risk offspring may be indicative of a biomarker for later psychopathology that is either inherited or altered due to environmental stress (Duffy et al., 2012).

Despite documented risks for the OBD, few preventative interventions for this high-risk population have been developed, and none have attempted to alter HPA axis functioning. The present study aimed to determine whether a prevention program designed to improve family functioning and decrease stress in the home would alter HPA axis functioning in the OBD. The study used a skills-based preventative intervention, entitled *Reducing Unwanted Stress in the Home (RUSH)*, which targeted parents with BD and their children (Serravalle et al., 2021). Drawing from Family-Focused Therapy (FFT; Miklowitz et al., 2011) and validated stress-reduction interventions (Abramowitz, 2012), the program aimed to provide parents and their children with stress-management techniques and to strengthen various domains of family functioning, including communication, conflict resolution, consistency, and organization. Unlike other interventions for the OBD (Miklowitz et al., 2011), the RUSH program was designed to target non-symptomatic at-risk offspring in childhood, prior to the development of affective symptoms.

The present proof-of-concept study used a quasi-experimental design with an intervention arm for families with a parent having BD and an assessment-only arm for control offspring being raised by parents with no history of affective disorder. We assessed prevention-related changes to three indices of HPA axis functioning: CAR, total daily output, and diurnal slope. We also examined whether changes to HPA axis functioning were influenced by children's baseline

internalizing symptoms, as the efficacy of past psychological interventions have been found to be dependent on the presence of psychological disturbances at baseline (Perich & Mitchell, 2019). Furthermore, we examined whether changes to the family environment (conflict, cohesion, expressiveness, organization, and control), influenced the degree of change in HPA axis functioning in the OBD.

It was hypothesized that HPA axis functioning would be more dysregulated in the OBD compared to controls, evident through elevated CAR and total daily output, and blunted diurnal slope at baseline. It was also hypothesized that OBD exposed to the RUSH program would display adaptive changes in HPA axis functioning, evident by a reduction in CAR and total daily output, and a steepening of diurnal slope across time. Such findings were expected to be moderated by offspring's baseline internalizing symptoms, such that children with higher internalizing scores at baseline would experience the greatest gains associated with exposure to RUSH. Finally, it was hypothesized that intervention-related improvements to the family environment would be associated with greater adaptive changes in offspring's HPA axis functioning.

Methods

Participants

Families having a parent diagnosed with BD were recruited and enrolled in the RUSH prevention program. At-risk families were recruited from the Montreal region through online and newspaper advertisements, in addition to local hospital clinics and patient support groups. To be eligible to participate in the RUSH program, parents had to meet diagnostic criteria for bipolar disorder (type I or II) according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV). Control families where neither parent met criteria for a current axis I

diagnosis or had suffered a past episode of major depressive disorder, mania, or hypomania were also recruited using similar advertisements within the same geographical region. All participating families had to have at least one biological offspring between 6 and 11 years of age and had to be fluent in either French or English. Children with a past or present diagnosis of an affective disorder, psychotic, or pervasive developmental disorder, or those with an intellectual or chronic physical disorder were excluded.

At baseline, a total of 66 children were recruited into the study. Following recruitment, 3 OBD withdrew from the study, while 5 OBD did not provide data beyond the first phase of testing. With respect to controls, 3 participants did not provide data beyond the first phase of testing. These 11 children were subsequently removed from the sample. The final sample consisted of 55 children (female; 52.7%) who were between 5 years 9 months to 12 years 6 months of age at initial recruitment (M=8.4 years, SD = 1.8) from a total of 45 families. Of the total sample, 26 children (female, 46.2%) comprised the OBD group and came from a total of 20 families, while the remaining 29 children (female, 58.6%) comprised the control group and came from a total of 25 families. See Table 1 for complete sample demographics.

Measures

Parent mental health

The Structured Clinical Interview for DSM-IV-R (SCID-I; First et al., 2002) is a semi-structured diagnostic clinical interview that was administered to assess past and present axis I mental disorders in parents. The SCID-I has been found to have moderate to excellent inter-rater reliability with kappa values ranging from .66 to .81 for affective disorders (Lobbestael et al., 2011).

Offspring emotional and behavioral functioning

At the beginning of the study, the Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version (K-SADS-PL; Kaufman et al., 1997) was administered to parents to assess offspring's past and present mental health disorders and to ensure their eligibility.

Children's behavioral and emotional functioning was assessed using the Parent Rating Scales-Child form (PRS-C; 160 items) of the Behavior Assessment System for Children, Second Edition (BASC-2; Reynolds & Kamphaus, 2004). Only the internalizing composite was used in the present study. Psychometric data pertaining to the measure demonstrate its high internal consistency and test-retest reliability, with alpha coefficients on the composites and scales exceeding 0.80 (Reynolds, 2010).

Family environment

Functioning of the family environment was assessed using the Family Environment Scale (FES; Moos & Moos, 1994), a 90-item self-report questionnaire. Only scores assessing conflict, cohesion, expressiveness, control, and organization were used. Cohesion, conflict, and expressiveness reflect relationship dimensions, assessing the degree to which family members are helpful and supportive of each other, the extent of anger and aggression expression within the family, and the degree to which members are encouraged to directly express their feelings, respectively (Moos & Moos, 2002). Organization and control reflect systems maintenance dimensions, assessing the importance of order and structure within the family and the enforcement and rigidity of role boundaries and rules/procedures (Moos & Moos, 2002). Psychometric properties of the scale suggest good validity and reliability (Moos & Moos, 1994). Absolute change scores from phase one to two were computed for each indicator of family

functioning and used as a marker of the RUSH program's efficacy in modifying the family environment.

Socioeconomic status (SES) was computed for each family based on maternal and/or paternal level of education and employment utilizing the Hollingshead Index criteria (Hollingshead, 1973).

Offspring salivary cortisol

At each assessment phase, offspring salivary cortisol was measured at six times across two consecutive weekend days: awakening, 30-minutes, and 60-minutes post-awakening, and at 13h00, 15h00, and 20h00 or bedtime. Saliva was expressed directly into polypropylene mini 6 ml vials (with a straw if needed). Parents were instructed to have their children refrain from eating or drinking 30 minutes prior to the collection of each sample and to record the time at which samples were collected. In addition, sampling vials were stored in larger vials with time-stamping micro-circuitry in the cap to automatically record the time at which the cap was opened and closed. Both self-report and time-stamping recordings were used to obtain a measure of sampling compliance. Saliva samples were stored at Concordia University in a -20°C freezer and then transported to the Douglas Mental Health University Institute (Montreal, Canada) to be assayed, in duplicate, for cortisol using a sensitive commercial enzyme immunoassay kit from Salimetrics (State College, Pennsylvania). The sensitivity of the assay was set at 0.012 µg/dl. The intra- and inter-assay coefficients of variability were 4.80% and 6.99%, respectively, across all four phases of testing.

Due to positive skew, cortisol values across the four phases were transformed using a natural log transformation. Outlier cortisol values were then corrected by winsorizing values to three standard deviations from the mean. CAR was computed with the three morning cortisol

samples using the Area Under the Curve with respect to increase formula (AUCi; Pruessner et al., 2003). Total daily output, using all cortisol samples, was computed using the Area under the Curve with respect to ground formula (AUCg; Pruessner et al., 2003). Diurnal slope was computed utilizing samples collected from 30-minutes post-awakening to bedtime. To facilitate visualization of significant results, slope values were multiplied by a factor of 100. Cortisol outcomes were averaged across the two days of sampling for each phase of testing to reduce intra-individual variability and provide more reliable estimates of cortisol secretory patterns.

Sampling compliance was computed by summing the total amount of time (in minutes) that participants' saliva sampling deviated from the designated collection time (e.g., 13h00, 15h00, and 20h00) for each cortisol sample. This value was averaged over the two days of sampling and the number of phases completed.

Procedures

Following a brief telephone screening, families were invited to the laboratory to undergo a diagnostic assessment. Index parents from the RUSH program and control parents participated in assessments over four phases: pre-, post-, and 3- and 6-months post-prevention. At each phase, families were invited to the laboratory to complete comprehensive assessments and were provided with collection materials to sample saliva from their children. For the present study, only data pertaining to cortisol, family environment, and child internalizing symptoms were included. Prior to participation, voluntary informed consent and assent was obtained from the parents and children, respectively. At the end of each phase of testing, parents were remunerated between $80 to $100 CAD, while children received a small toy for their participation. The study was approved by the Human Research Ethic Committee of Concordia University (Montreal, Canada).

Reducing Unwanted Stress in the Home (RUSH) protocol

The RUSH prevention program consisted of 12 manual-based, closed weekly group sessions; parent and child sessions were run separately but simultaneously. Sessions were two hours in length and incorporated 60-minutes of free-play time within the child sessions. The program was developed by the study's authors but drew upon empirically supported interventions on stress management, family functioning and relationships, and parenting skills (Abramowitz, 2012; Kendall & Hedtke, 2006; Miklowitz et al., 2011; Severe, 2000). Parent sessions focused psycho-education about stress, problem-solving, effective communication, improving organization in the home, and managing child behavior. Child sessions focused on age-appropriate coping strategies, cognitive restructuring, problem-solving, emotion labelling, relaxation, and assertiveness. A review of the program and its administration has been published elsewhere (Serravalle et al., 2021).

Statistical analyses

Hierarchical Linear Modeling (HLM; Raudenbush, 2004) was used to compute a growth curve model estimating whether intervention group (RUSH or Control) predicted HPA axis functioning (CAR, total daily output, and diurnal slope). The model involved the estimation of cortisol outcomes as a function of intervention group and baseline internalizing symptoms. At Level 1, we estimated the variance in offspring's cortisol outcome across the four phases of testing as a function of an intercept, uncentered scores of time, and a residual term. Given that the intercept was entered uncentered, it represented the cortisol outcome at baseline. The coefficient of primary interest was the estimation of the slope (time), which examined changes in cortisol markers across time. At Level 2, intervention group and baseline internalizing symptoms were entered as predictors of intercept and slope. The model also included those covariates (e.g.,

age, SES) that correlated significantly with the cortisol outcome variables. An interaction term was finally entered between intervention group and baseline internalizing symptoms.

A second growth-curve model was computed to estimate the effects of the RUSH program on HPA axis functioning across time as a function of change to the home environment. As we were interested in examining whether improvements to family functioning attributable to the RUSH program moderated changes to HPA axis functioning, only those data belonging to the OBD were examined. Level 1 for model two was similar to that of model one, estimating the variance in offspring's cortisol outcomes across time. At Level 2, however, we predicted the intercept and slope of cortisol as a function of change in the family environment, with respect to changes in control, conflict, cohesion, expressiveness, and organization, in addition to the covariates. Separate models were computed for each index of family functioning. Significant predictors on the time slope were followed-up by estimating the effects of time on the cortisol outcomes at the mean and one standard deviation above and below family environment change scores.

All Level 2 predictor variables were standardized prior to conducting the analyses. The reported effects are based on models using restricted maximum likelihood estimation and robust standard errors.

Results

Preliminary analyses

Variable descriptives are presented in Table 1 and zero-order Pearson correlations of study variables are presented in Table 2. With respect to the covariates, total daily output at baseline was positively associated with SES (p = .028), such that lower SES was associated with lower cortisol output across the day measured at the first phase of testing.

Predicting change in cortisol

Effects of the intervention group on cortisol over time

HLM analyses were conducted to estimate the effect of intervention group (RUSH or Control) on the three cortisol outcomes: CAR, total daily output, and diurnal slope, as presented in Table 3. The Level 1 model for total daily output and diurnal slope found a significant effect for the intercept, indicating that participants' daily cortisol output ($p < .001$) and diurnal slope ($p < .001$) at baseline were significantly different from zero. However, this was not the case for the CAR. With respect to the time slope, only the diurnal slope was statistically different from zero ($p < .05$), implying that the diurnal slope changed across time for the entire sample. Finally, results from the Level 1 model did not display significant variance around participants' baseline intercept of CARi, $\chi^2 = 53.04$, $df = 54$, *ns*, nor around the slope of CAR $\chi^2 = 57.64$, $df = 54$, *ns.* With respect to total daily output (AUCg), significant variance was found around the intercept (baseline), $\chi^2 = 147.74$, $df = 54$, $p < .001$, and slope, $\chi^2 = 71.73$, $df = 54$, $p < .05$. Similarly, with respect to diurnal slope, significant variance was found around the intercept (baseline), $\chi^2 = 162.26$, $df = 54$, $p < .001$, and slope, $\chi^2 = 102.42$, $df = 54$, $p < .001$. The lack of variance at the intercept or on the time slope for CAR may be attributed to the relatively small sample size, which potentially underpowered the analyses. Given this limitation and our theoretical interest, Level 2 analyses proceeded estimating slope across time for all diurnal cortisol indices.

In the Level 2 model, we predicted the observed variance in the intercept and slope of participants' CAR, total daily output, and diurnal slope. SES, the only covariate entered, positively predicted the intercept of daily cortisol output, such that lower SES scores were associated with lower total daily output at baseline (coefficient = 5.18, *SE*=2.21, *T-ratio* = 2.35, $p < .05$). With respect to the main effects of intervention group and internalizing scores measured

at baseline, neither significantly predicted the cortisol outcomes at baseline (intercept) or across time (slope). Similarly, the final step of the analyses did not find the intervention group to significantly interact with internalizing scores at baseline to predict cortisol outcomes at either baseline (intercept) or across time (slope).

Moderating effects of the family environment on cortisol change in response to RUSH

Table 4 summarizes the results of the HLM analyses that estimated cortisol outcomes in those participants who participated in the RUSH prevention program controlling for SES. Change in the family environment, with respect to organization, cohesion, control, expressiveness, and conflict from phase one to two were included in separate models. The significance and direction of effects for the Level 1 model were similar to the results of the HLM analyses presented in section 3.2.1, such that participants' total daily output ($p < .001$) and diurnal slope ($p < .001$) at baseline were significantly different from zero. None of the cortisol outcomes were significant on the time slope, suggesting that the OBD demonstrated relative stability in their cortisol outcomes across the duration of the study. Results from the Level 1 model did not display significant variance around participants' baseline intercept of CARi, $\chi^2 = 16.99$, $df = 25$, $p > .50$, however, variance around the slope of CAR approached significance $\chi^2 = 35.67$, $df = 25$, $p = .07$. With respect to total daily output (AUCg), significant variance was found around the intercept (baseline), $\chi^2 = 60.53$, $df = 25$, $p < .001$, and slope, $\chi^2 = 40.79$, $df = 25$, $p < .05$. Finally, with respect to diurnal slope, significant variance was found around the intercept (baseline), $\chi^2 = 71.13$, $df = 25$, $p < .001$, and slope, $\chi^2 = 64.10$, $df = 25$, $p < .001$.

In the Level 2 model, lower SES at baseline was predictive of lower daily cortisol output at baseline and an increase in daily cortisol output across the duration of the study. With respect to diurnal cortisol slope, lower SES at baseline was predictive of a flattened diurnal slope at

baseline and increasingly steeper slope across time. The observed variance in the intercept and slope of participants' cortisol outcomes were predicted by the degree of change in the family environment with respect to organization and cohesion. Change in family organization was found to significantly predict participants' CAR ($p < .01$), total daily output ($p < .05$), and diurnal slope ($p < .01$) on the time slope. The models explained 25.69%, 28.46%, and 43.25% of the total variance, respectively. With respect to cohesion, an improvement in family cohesion following the RUSH prevention program was also found to significantly predict participants' CAR ($p < .001$) and, to a lesser degree, diurnal slope ($p = .064$) across time (slope). These models accounted for 22.90% and 26.76% of the total variance, respectively.

To illustrate the significant relationship between change in family environment and cortisol outcomes across time, we applied recommended growth-curve techniques (Preacher et al., 2006). Associations between the cortisol outcomes (CAR, total daily output, and diurnal slope) and time were plotted at the mean and one standard deviation above and below the mean change in family organization and cohesion scores. As seen in Figure 1a, offspring in the RUSH program who experienced a heightened change in organization in their family environment went on to experience a significant elevation in CAR across the duration of the study (coefficient = 0.32, *SE* = 0.14), *T-ratio* = 2.31, $p < 0.05$). Conversely, offspring exposed to the prevention group, but who did not experience a corresponding change to the level of organization within the home, exhibited a non-significant decline in their CAR across time (coefficient = -0.16, *SE* = 0.08, *T-ratio* = -1.91, $p = 0.068$). A similar pattern was observed in predicting total daily output (Figure 1b), such that offspring who experienced an elevation in organization in the home went on to secrete greater cortisol over the course of the day across the duration of the study (coefficient = 1.40, *SE* = 0.59, *T-ratio* = 2.37, $p < 0.05$). Finally, an improvement in organization

in the home was also associated with a steepening of diurnal slope (Figure 1c). Diurnal slope became increasingly steep as the change in organization increased from average (coefficient = -0.04, *SE* = 0.02, *T-ratio* = -2.32, $p < 0.05$) to high (coefficient = -0.09, *SE* = 0.03, *T-ratio* = -3.64, $p < 0.001$). Overall, changes in the home environment with respect to improved organization resulted in greater changes to participants' cortisol levels over time.

Similar findings with respect to change in cohesion in the family environment are depicted in Figure 2. Improvements in family cohesions in response to the RUSH prevention program were associated with a significant elevation in participants' CAR (coefficient = 0.31, *SE* = 0.11, *T-ratio* = 2.70, $p < 0.01$). Furthermore, a steepening of diurnal slope across time was observed as changes in family cohesion increased from average (coefficient = -0.04, *SE* = 0.02, *T-ratio* = -2.08, $p < 0.05$) to high (coefficient = -0.07, *SE* = 0.03, *T-ratio* = -2.39, $p < 0.05$). The opposite association was observed for individuals who experienced a decrease in family cohesion following exposure to the prevention program, such that CAR significantly declined across the duration of the study (coefficient = -0.18, *SE* = 0.08, *T-ratio* = -2.29, $p < 0.05$). Overall, the level of change in family cohesion also influenced offspring's' cortisol outcomes, such that greater changes in family cohesion were accompanied by greater changes in offspring's cortisol outcomes.

The relationship between change in family conflict, control, and expressiveness with indices of cortisol secretion were also examined. No significant findings were observed for cortisol outcomes at baseline or across time (data not shown).

Discussion

The present study is the first of its kind to examine the effects of a skills-based, family-targeted prevention program (RUSH) on HPA axis functioning in the OBD in childhood, prior to

the development of symptoms of an affective disorder. Given that the HPA axis has been implicated in affective disorders in at-risk populations (Ellenbogen et al., 2011; Halligan et al., 2007), examining the effects of an intervention on HPA axis functioning sheds light onto potential markers of program effectiveness, or a program's ability to apply therapeutic effects 'under the skin' in at-risk populations. The primary goal of the present study was to examine the effects of RUSH on HPA axis functioning in the OBD, furthermore, to compare HPA functioning to that of healthy control children who did not participate in the program but underwent identical repeated assessments. There were two key findings. First, contrary to predictions, no group differences between the OBD and healthy controls were observed on any of the indices of HPA functioning (CAR, total daily output, diurnal slope) at baseline or across the duration of the study. Second, the OBD whose families benefited from the preventative intervention by showing improved organization or cohesion, exhibited significant changes on measures of HPA functioning, suggestive of intervention-related adaptive changes in neuroendocrine functioning over time.

The null findings at baseline, with respect to cortisol outcomes, suggest that the OBD in childhood did not display abnormalities in HPA axis functioning as initially hypothesized. The absence of group differences in daytime cortisol levels run contrary to past reports, whereby adolescents and young adults at risk for the development of affective disorders exhibited elevated morning and afternoon cortisol levels in comparison to offspring of parents with no psychopathology (Ellenbogen et al., 2006; Ellenbogen et al., 2010; Mannie et al., 2007). While elevated HPA axis functioning may be distinctive of adults having an affective disorder and the OBD in adolescence and early adulthood, there are no studies of cortisol levels or HPA functioning, to the best of our knowledge, in the OBD in early or middle childhood (Ellenbogen

et al., 2019; Klimes-Dougan et al., 2022). Thus, the OBD may not yet exhibit noticeable alterations in HPA axis functioning in childhood or the changes in HPA functioning in childhood may be different than what has been recorded in adolescence and adulthood. As alterations in HPA functioning may arise from extreme or chronic stress exposure (Southwick et al., 2005), the lack of detectable group differences in the present sample may stem from the reduced duration of environmental stress exposure due to the child's young age. In addition, null baseline results may also be related to puberty-related changes to the developing HPA axis. Hankin et al. (2010) found the pattern of HPA axis reactivity to psychosocial stressors in at-risk, dysphoric children and adolescents to depend on their stage of pubertal development. While postpubertal, dysphoric adolescents displayed cortisol hyperreactivity in response to a psychosocial stressor, prepubertal children (i.e., preschoolers and third graders) displayed a pattern of cortisol hyporeactivity. Furthermore, a pattern of cortisol hyporeactivity in at-risk prepubertal females has been found to predict later major depressive disorder as youth entered adolescence (Colich et al., 2015). Thus, the absence of significant baseline cortisol differences in the present study compared to earlier studies in at-risk adolescents may be related to the coupling of the HPA and gonadal (responsible for the release of sex hormones) axes, whereby hyporeactivity of the HPA axis in at-risk offspring reflects low circulating sex hormones associated with participant's early pubertal development (Shirtcliff et al., 2015).

In addition to the absence of group differences at baseline, there was no evidence that participation in the RUSH program altered indices of HPA functioning across time. Our findings run contrary to past preventative intervention studies, whereby at-risk children (e.g., institutionalized, involved with Child Protective Services, or parentally bereaved) enrolled in a family-based intervention exhibited significant changes in their HPA axis functioning following

completion of the intervention and at follow-up (for review see Slopen et al., 2014). Children enrolled in such programs have demonstrated cortisol levels, diurnal cortisol profiles (e.g., slope, AUC), and cortisol reactivity patterns that significantly differed from at-risk controls receiving care as usual, and more closely resembled that of low-risk community controls (Slopen et al., 2014). While unexpected, the absence of change in HPA axis functioning in response to RUSH may be attributable to the fact that not all families garnered similar therapeutic benefits from the intervention applied. Furthermore, we did not find baseline internalizing symptoms in offspring to predict change in HPA axis functioning in response to the RUSH program. These findings run contrary to past studies that have found children with elevated symptomatology at baseline to garner greater therapeutic effects from preventative interventions (Perich & Mitchell, 2019).

As a secondary goal, we examined whether the effects of the RUSH program on offspring's HPA axis functioning varied by the degree to which change occurred in the family environment. Improvements in family organization following the RUSH program were associated with changes on all indices of HPA axis functioning across time, including an increase in CAR and total daily output, and a steepening of the cortisol diurnal slope. With respect to family cohesion, similar changes in cortisol outcomes were observed in offspring's CAR and, to a lesser degree, their cortisol diurnal slope from baseline to the final follow-up. Conversely, a worsening or an absence of change in family organization and cohesion following the RUSH program were associated with a decrease in CAR over time in the OBD. Changes in HPA functioning in response to improvements in family functioning elicited by the RUSH preventative intervention highlight the extent to which family organization and cohesion may be affected in at-risk families, and how such effects may consequently alter underlying biological stress-regulatory systems. The present results add to the existing literature highlighting the

impact of the early family environment on offspring HPA activity. Lower family socioeconomic status (SES), thought to be accompanied by exposure to more frequent and severe psychosocial and physical stressors, has been found to influence HPA functioning in children and adolescents (Koss & Gunnar, 2018), with children from lower SES backgrounds demonstrating evidence of both higher and lower cortisol levels compared to their elevated SES counterparts (Chen et al., 2010; Chen & Paterson, 2006). Additional markers of family functioning, such as perceived level of family chaos, have also been found to mediate the association between SES and cortisol such that lower SES predicted greater cortisol secretion in families with greater chaos (Chen et al., 2010). Luecken and Appelhans (2006) also found the quality of the family environment, as measured by self-reported abusive treatment and family conflict, to moderate the impact of early parental loss on offspring's cortisol reactivity. Collectively, these results attest to the impact that the early environment can have on shaping development and functioning of the HPA axis, both directly and indirectly.

Although we predicted that the RUSH program would decrease CAR and total cortisol output and dampen diurnal slope, based on studies of adolescent and young adult OBD demonstrating high cortisol levels, we found that the RUSH program had the opposite effect in OBD during childhood. OBD exposed to the RUSH program who experienced corresponding improvements to their family environment demonstrated cortisol levels indicative of heightened HPA functioning and cortisol output (i.e., elevated cortisol diurnal profiles and a steepening of their cortisol slope). While unexpected, our results align with past intervention studies that found evidence of increased diurnal cortisol levels (Fisher et al., 2007) and steepening of the diurnal slope (Bernard et al., 2015) in at-risk children following exposure to family-based psychosocial interventions. As decreased cortisol levels and dampened diurnal rhythms have been associated

with poorer mental health outcomes (Shirtcliff & Essex, 2008), behavioural problems (Luecken et al., 2010), and health problems (Adam et al., 2017), increased cortisol levels and steepening of the diurnal slope in response to improvements in family cohesion and organization, may represent improvements in OBD's HPA axis functioning. Overall, the absence of direct effects of the RUSH intervention on indices of HPA axis functioning highlight the difficulties in changing neuroendocrine function through a time-limited preventative intervention. However, our results also demonstrate that a family-focused intervention that elicits improvements to the family environment may produce adaptive changes in HPA axis functioning in at-risk offspring, thus reducing their risk for later life adverse outcomes.

It is important to note that the significant findings from our study were linked to changes in organization and cohesion, rather than conflict, control, or expressiveness in the family environment. These findings corroborate past studies whereby OBD exposed to low structure in the home, encompassing organization and consistency, were more likely to display behavioural and emotional problems (Iacono et al., 2018) and elevated cortisol reactivity to a psychosocial stressor and at awakening (Ellenbogen & Hodgins, 2009). Our results add to the literature, implicating family organization and cohesion as potential pathways by which BD in parents impacts the family environment and subsequently the development and functioning of offspring's HPA axis, and their risk for later mental health difficulties.

Several study limitations warrant consideration. First, the sample size was small, limiting statistical power. However, the small sample was assessed at four time points and used multilevel modeling with restricted maximum likelihood estimation to minimize this limitation. In addition, the sample size in the present study falls in line with past prevention studies that have examined other at-risk populations (Urizar & Munoz, 2011). Second, the present study did

not utilize a randomized controlled trial (RCT) design, the gold-standard for examining the effectiveness of interventions. Our proof-of-concept design was used because of the low prevalence of parents having BD with children within a small age range (6 to 11 years). Although the study design allowed for direct comparison of the OBD and controls over time, it did not test whether the RUSH intervention families would fare better than a waitlist or active control intervention. Thus, there is a need to continue this line of research utilizing larger sample sizes and an RCT design. Third, pubertal stage, which has been found to influence functioning of the HPA axis via coupling with the gonadal axis, was not measure in the present study (Shirtcliff et al., 2015). However, the present sample of school-aged children was purposefully selected to minimize the impact of puberty on measured HPA axis functioning. Finally, the present study did not include an objective measure of children's awakening time to ensure little to no delay between awakening time and the collection of children's first morning saliva sample. In addition to time-stamping bottles and self-report tracking, future studies should incorporate movement tracking devices such as wrist actigraphy to verify the timing of first-morning sampling, as brief delays between awakening and saliva collection have been found to affect the validity of the CAR assessment (Stalder et al., 2016).

Despite these limitations, results from the present study offer evidence that a family-based preventative intervention program that aims to improve the family environment, particularly levels of organization and cohesion, may lead to adaptive changes in HPA axis functioning. The findings highlight how teaching parents the skills to better manage family-related stress in the home, as well as providing children with the skills to better cope with stress, can elicit changes in the family environment that ameliorate putative neuroendocrine risk factors in high-risk children. If the present findings can be replicated in the context of RCTs, future

studies would need to assess whether intervention-related changes in HPA functioning decrease the development of mental disorders in high-risk children.

Table 1
Means, Standard deviations, Range, and Frequencies of study variables (N=55).

Variables	Mean (SD) or Frequency count (%); Range	
	OBD Group	Control Group
Cortisol (P1)		
CAR increase	-0.20 (2.36)	-0.27 (2.85)
AUC ground	39.55 (23.86)	40.77 (20.80)
Slope	-0.008 (0.008)	-0.008 (0.008)
Offspring Behaviour (P1)		
Internalizing	25.12 (10.01)	21.48 (11.14)
FES (P1)		
Organization	5.00 (2.23)	6.76 (1.35)
Control	3.58 (1.90)	4.28 (1.62)
Conflict	3.81 (2.42)	2.07 (1.89)
Cohesion	6.62 (1.30)	7.17 (1.20)
Expressiveness	6.15 (1.12)	7.00 (1.13)
Change in FES (P1 – P2)		
△Organization	0.88 (1.70)	-0.21 (1.01)
△Control	-0.33 (1.34)	0.00 (1.41)
△Conflict	-0.08 (1.84)	-0.76 (1.27)
△Cohesion	0.83 (1.49)	0.83 (1.20)
△Expressiveness	0.33 (1.27)	0.24 (1.27)
Age in months (P1)	93.92 (22.03); 69-142	106.97 (19.11); 73-150
Intervention Group	26 (47.30%)	29 (52.70%)
Sex (female)	12 (46.20%)	17 (58.60%)
Socioeconomic status (SES)	9.23 (2.34); 5-12	9.69 (1.29); 7-12
Ethnicity		
White	39 (70.90%)	
Aboriginal	2 (3.60%)	
Black	5 (9.10%)	
East Asian	1 (1.80%)	
Hispanic/Latino/Latin-American	4 (7.30%)	
Middle Eastern/North African/ Central Asian	4 (7.30%)	

Notes. P = phase. CAR = cortisol awakening response. AUC = area under the curve. FES = Family Environment Scale. OBD = offspring of parents with bipolar disorder. SES – higher value indicates higher SES.

Table 2. Zero-order Pearson Correlations of main study variables (N=55).

	1	2	3	4	5	6	7	8	9	10	11	12
1. Intervention Group												
2. CAR AUCi (P1)	.014											
3. AUCg (P1)	-.028	.540**										
4. Slope (P1)	.032	-.656**	-.685**									
5. ΔFES Organization	.373**	-.053	.137	-.050								
6. ΔFES Control	-.122	.215	.089	-.018	-.026							
7. ΔFES Conflict	.215	.136	.090	-.051	-.110	.101						
8. ΔFES Cohesion	.002	-.124	.064	.024	.333*	.122	-.056					
9. ΔFES Expressiveness	.037	-.181	-.002	.020	.290*	-.318*	-.234	-.028				
10. Internalizing (P1)	.171	-.001	-.095	.112	.142	-.013	-.136	.052	.210			
11. Age (P1)	-.307*	.072	-.060	.013	.019	-.037	-.096	.167	.004	-.015		
12. SES	-.125	.121	.296*	-.208	.050	-.099	.040	-.115	.168	.163	-.145	
13. Compliance	.141	.082	-.247	.129	-.233	.075	.343*	.014	-.162	.127	.022	-.039

Notes. CAR – cortisol awakening response. AUCi – area under the curve with respect to increase. AUCg – area under the curve with respect to ground. P – phase. FES – family environment scale. Δ - change score from Phase 1 to Phase 2. SES – socioeconomic status.
* $p < .05$; ** $p < .01$.

Table 3. Effects of intervention group on diurnal cortisol levels over time.

	CAR(AUCi)				Daily cortisol output (AUCg)				Slope			
	Intercept (Baseline)		Slope (Time)		Intercept (Baseline)		Slope (Time)		Intercept (Baseline)		Slope (Time)	
	Coefficient (SE)	T-Ratio	Coefficient (SE)	T-Ratio	Coefficient (SE)	T-Ratio	Coefficient (SE)	T-Ratio	Coefficient (SE)	T-Ratio	Coefficient (SE)	T-Ratio
Level 1 (β_0; β_1)	-0.43 (0.28)	-1.53	0.09 (0.05)	1.70	41.59 (2.44)	17.03***	0.11 (0.32)	0.36	-0.87 (0.09)	-10.08***	-0.03 (0.01)	-2.37*
Level 2: Main effects												
Intercept	-0.43 (0.28)	-1.52	0.09 (0.05)	1.64	41.52 (2.35)	17.66***	0.15 (0.31)	0.48	-0.87 (0.08)	-10.23***	-0.03 (0.01)	-2.44*
Intervention Group	0.05 (0.29)	0.17	-0.01 (0.06)	-0.26	1.08 (2.55)	0.42	0.11 (0.37)	0.31	-0.03 (0.10)	-0.26	-0.00 (0.01)	-0.29
Internalizing (P1)	0.13 (0.26)	0.50	-0.08 (0.05)	-1.58	-1.20 (2.64)	-0.46	0.44 (0.41)	1.08	0.04 (0.11)	0.37	-0.01 (0.02)	-0.35
SES	0.14 (0.28)	0.49	-0.01 (0.07)	-0.09	5.18 (2.21)	2.35*	-0.72 (0.42)	-1.72	-0.13 (0.10)	-1.29	0.02 (0.02)	1.25
Level 2: Interaction effect												
Group x Internalizing	-0.31 (0.26)	-1.20	0.04 (0.05)	0.90	-2.68 (2.61)	-1.03	0.44 (0.42)	1.05	0.02 (0.10)	0.21	-0.00 (0.01)	-0.13

Notes. CAR – cortisol awakening response. AUC – area under the curve. SES – socioeconomic status. SE - standard error.
* $p < .05$; ** $p < .01$; ***$p < .001$.

Table 4. Effects of the family environment on diurnal cortisol levels across time.

	CAR AUCi				Daily AUCg				Slope			
	Intercept (Baseline)		Slope (Time)		Intercept (Baseline)		Slope (Time)		Intercept (Baseline)		Slope (Time)	
	Coefficient (SE)	T-Ratio	Coefficient (SE)	T-Ratio	Coefficient (SE)	T-Ratio	Coefficient (SE)	T-Ratio	Coefficient (SE)	T-Ratio	Coefficient (SE)	T-Ratio
Level 1 (b_0; b_1)	-0.37 (0.34)	-1.09	0.06 (0.09)	0.59	41.76 (3.58)	11.67***	0.45 (0.58)	0.77	-0.87 (0.12)	-7.03***	-0.04 (0.02)	-1.77
Level 2A: Main effects												
Intercept	-0.42 (0.33)	-1.27	0.08 (0.09)	0.88	41.55 (3.32)	12.53***	0.52 (0.52)	1.01	-0.86 (0.11)	-7.70***	-0.04 (0.02)	-2.32*
SES	0.39 (0.35)	1.11	-0.09 (0.10)	-0.94	7.37 (2.98)	2.47*	-1.33 (0.65)	-2.06*	-0.29 (0.12)	-2.36*	0.06 (0.02)	2.85**
△FES organization	-0.60 (0.22)	-2.67*	0.24 (0.07)	3.27**	-2.53 (3.67)	-0.69	0.88 (0.36)	2.45*	0.14 (0.10)	1.40	-0.05 (0.01)	-3.46**
Level 2B: Main effects												
Intercept	-0.39 (0.33)	-1.21	0.06 (0.09)	0.71	41.67 (3.12)	13.36***	0.47 (0.51)	0.91	-0.87 (0.11)	-8.06***	-0.04 (0.02)	-2.08*
SES	0.29 (0.37)	0.80	-0.06 (0.10)	-0.60	6.62 (3.09)	2.14*	-1.17 (0.66)	-1.79	-0.26 (0.12)	-2.06*	0.05 (0.02)	2.25*
△FES cohesion	-0.61 (0.20)	-3.11**	0.25 (0.05)	5.03***	-6.07 (2.15)	-2.82**	0.93 (0.57)	1.64	0.20 (0.09)	2.17*	-0.03 (0.01)	-1.95†

Notes. CAR – cortisol awakening response. AUC – area under the curve. SES – socioeconomic status. SE - standard error. △FES - change in family environment from P1 to P2.

† $p = .064$; * $p < .05$; ** $p < .01$; *** $p < .001$.

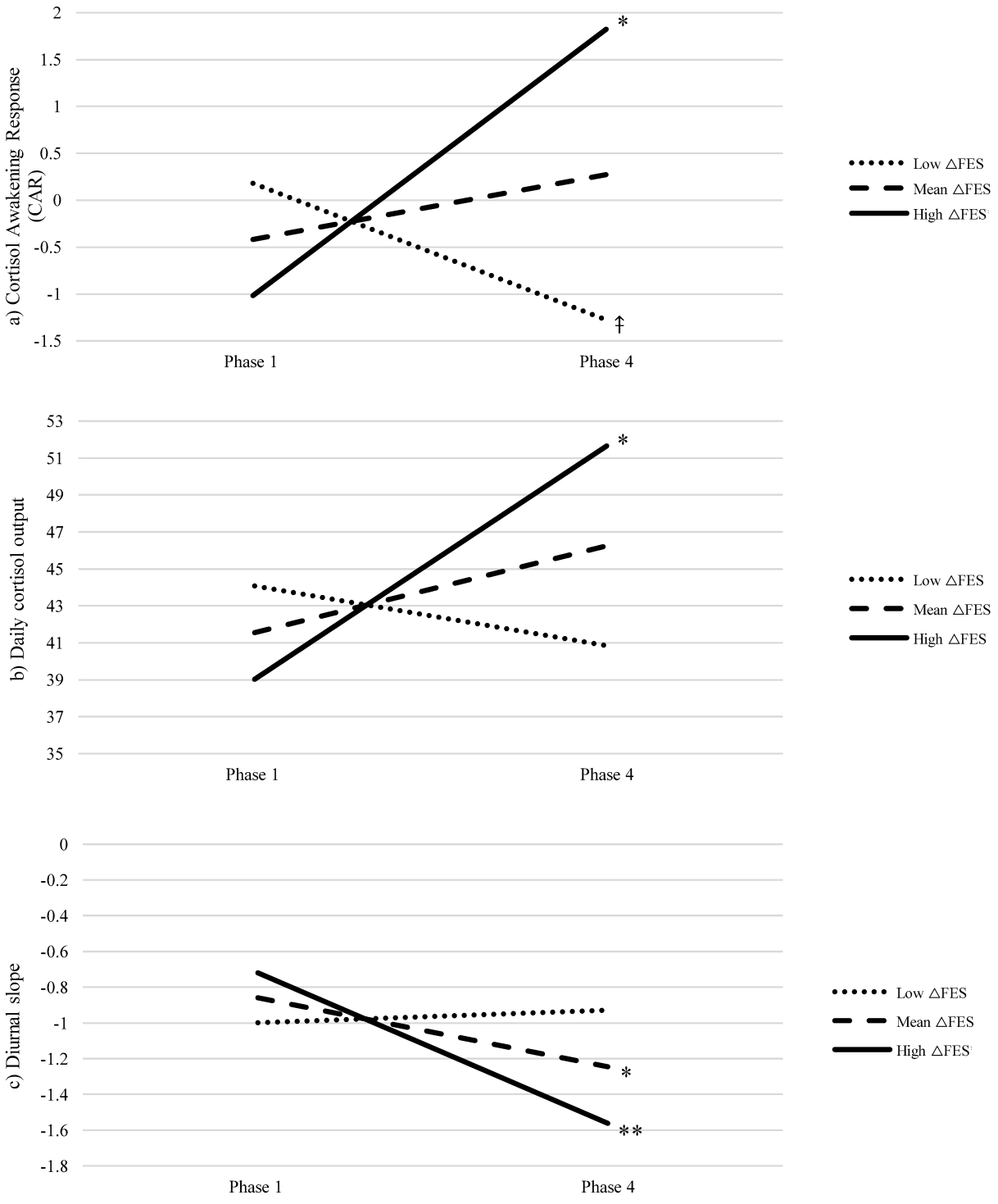

Figure 1. Effects of change in family environment with respect to organization, measured with the Family Environment Scale (FES), on the a) cortisol awakening response (CAR), b) daily cortisol output, and c) diurnal slope across time in offspring exposed to the RUSH prevention program.
† $p = .068$, * $p < .05$, ** $p < .01$.

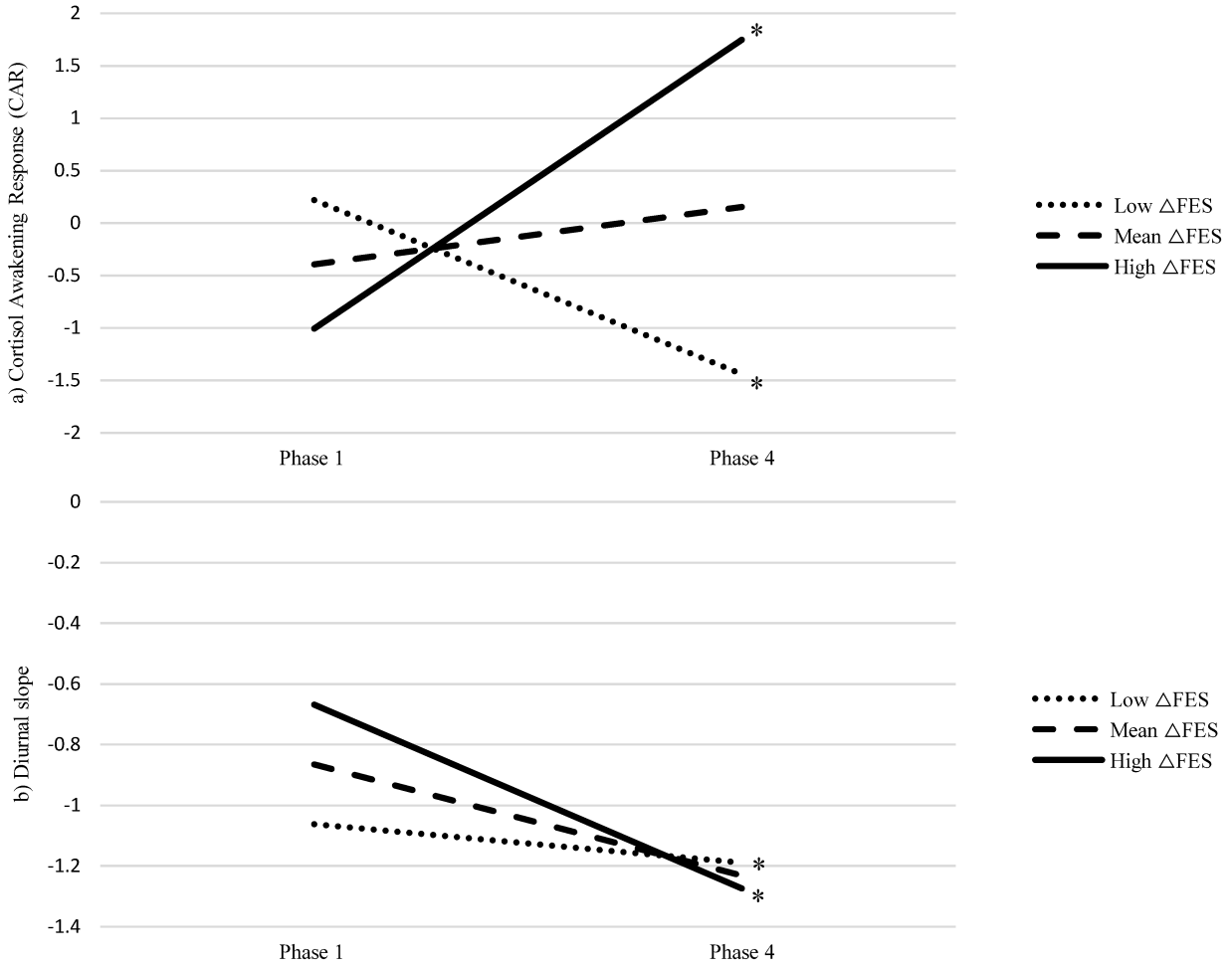

Figure 2. Effects of change in the family environment with respect to cohesion, measured with the Family Environment Scale (FES), on the a) cortisol awakening response (CAR) and b) diurnal slope across time in offspring exposed to the RUSH prevention program.
* $p < .05$.

Transition Paragraph 2

The RUSH prevention program was found to exert effects 'under the skin', altering diurnal HPA axis activity in OBD who experienced improvements in family functioning (i.e., organization and cohesion) following the program's completion. As dysregulated HPA axis functioning may underlie risk for affective disorders (Ellenbogen et al., 2011), our results suggest that appropriately timed preventive interventions may potentially alter regulation of the HPA axis, which in turn may influence the developmental course of psychopathology. Further research using larger sample sizes in an RCT design, different at-risk samples, and incorporating a longer follow-up is required to determine whether RUSH-related changes to HPA axis function translate into improved mental health outcomes (i.e., reduced rates of affective disorders, lower conversion rates to BD, etc.) in the long-term.

Results in the field thus far attest to the HPA axis' sensitivity to environmental change, in contexts of both adversity (Raymond et al., 2018) and enrichment (as in study 2). As such, the next study of this dissertation sought to assess whether indices of HPA axis function could act as a marker of individual sensitivity to changes in the environment. Baseline HPA axis function was measured in the OBD to determine its role in predicating offspring's internalizing and externalizing symptoms in response to the RUSH program. Results from the study are vital to the development of future preventive interventions, particularly the consideration of how biopsychosocial variables may influence the response to an intervention. Collecting and applying such information to adapt programming to needs of the individual has the potential to increase program effectiveness and warrants continued investigation.

Chapter 4: Low cortisol levels in children of parents with bipolar disorder predicts their response to a preventative intervention

Citation: Yong Ping, E., Herriot, H., Iacono, V., Serravalle, L., & Ellenbogen, M.A. Low cortisol levels in children of parents with bipolar disorder predicts their response to a preventative intervention. (Manuscript in preparation for submission). Department of Psychology, Concordia University.

Contributions: This manuscript was conducted using data previously collected for the Reducing Unwanted Stress in the Home (RUSH) prevention study, which was initiated and organized by Drs. Ellenbogen and Iacono, and Lisa Serravalle. In collaboration with Dr. Ellenbogen, Erin Yong Ping conceptualized the research question and the selection of the necessary data to answer the research question. Dr. Herriot provided support in completing and interpreting the statistical analyses. Under the supervision of Dr. Ellenbogen, Erin Yong Ping interpreted the data and drafted the manuscript. All authors participated in reviewing and editing the manuscript.

Abstract

Background: Relatively few prevention programs have been developed to target offspring of parents with bipolar disorder (OBD) during childhood, prior to the onset of affective disorders. Increasing research indicates that biological markers, including stress neurobiology, may influence individual sensitivity to a preventative intervention. The present study aimed to examine the effects of a family-based preventative intervention entitled Reducing Unwanted Stress in the Home (RUSH) on offspring internalizing and externalizing behaviours as a function of underlying baseline diurnal cortisol patterns.

Methods: Twenty-six OBD were recruited and enrolled in RUSH, while 29 healthy offspring whose parents did not have an affective disorder were recruited but did not complete the prevention program. Both groups of families completed assessments that measured child internalizing and externalizing behaviours, as well as their salivary cortisol levels, at four phases: baseline, post-intervention, and 3- and 6-months post-interventions.

Results: Hierarchical Linear Modelling found that OBD with lower cortisol awakening response and total cortisol output, as well as flatter diurnal cortisol slopes at baseline, exhibited significant decreases in their internalizing behaviours following the RUSH program up to 6-months post-intervention.

Discussion: In sum, blunted HPA axis function prior to the intervention may be a biological marker identifying those OBD most likely to benefit from an early prevention program that targets the family environment and individual stress-coping abilities. Because the sample size was small and this was not a randomized controlled trial, replication of this novel finding is needed.

Introduction

Offspring of parents with bipolar disorder (OBD) have been found to be at elevated risk for emotional, behavioural, and psychosocial problems across childhood and into adulthood (Lau, Hawes, Hunt, Frankland, Roberts, & Mitchell, 2018). While it is well known that the transmission of BD from parents to offspring is strongly genetic in nature (McGuffin et al., 2003), there is increasing evidence that the family environment, including parenting behaviours, influence developmental outcomes in the OBD (Stapp et al., 2020). Compared to healthy controls, the home environment of the OBD has been characterized by elevated levels of conflict and control, and lower levels of expressed emotion, organization, and cohesion (Barron et al., 2014; Chang et al., 2001; Ferreira et al., 2013; Meyer et al., 2006). With respect to parenting, adults with BD have been found to use less effective styles of parenting and negative communication styles, and to display less care and more overprotection (conceptualized as 'affectionless control') compared to parents with other or no mental health disorders (Gomes et al., 2015; Iacono et al., 2018). Exposure to such environments has been found to increase risk for negative outcomes in the OBD, including elevated rates of psychopathology across the lifespan (Ferreira et al., 2013). Iacono et al. (2018) found that low structure (organization and consistency in the home) in middle childhood was associated with concurrent elevations of internalizing and externalizing difficulties in OBD, while low control (inconsistent use of disciplinary practices) in middle childhood was associated win increased symptoms of depression and substance use problems when the offspring were in early adulthood. Along a similar vein, a history of childhood trauma or adversity in adults diagnosed with BD has been associated with worse clinical outcomes and greater functional impairment compared to individuals without a history of trauma (Farias et al., 2019; Palmier-Claus et al., 2016). Collectively, these results highlight the

impact of the early environment and early adverse experiences on the development of affective disorders and other negative outcomes in the OBD.

Despite growing evidence of the importance of the early environment in the OBD, there is little research on family-based preventative interventions in this population. Prevention programs that aim to improve functioning within the family environment may reduce risk for later psychopathology and adverse psychosocial functioning in the OBD, reducing the burden of disease in the affected individual, as well as society at large (Gore et al., 2011). Despite the growing need for early prevention, relatively few such programs have been developed and studied. *Family Focused Therapy* (FFT; see review Miklowitz & Chung, 2016), originally developed as an intervention for children and adults with BD, was adapted for the OBD (for full review see; Miklowitz et al., 2011). Studies examining the efficacy of FFT in symptomatic OBD youth have found the intervention to improve symptoms of depression, (hypo)mania, and psychosocial functioning (Miklowitz et al., 2011). FFT has also been associated with longer intervals between recovery and re-emergence of a depressive episode compared to those in an educational control group (Miklowitz, Schneck, et al., 2020). The program, however, has not targeted the OBD during childhood. Childhood represents a critical stage of development for the OBD that is often marked by elevated behavioural, mood, and anxiety disorders (Ellenbogen & Hodgins, 2004; Hirshfeld-Becker et al., 2006) that subsequently increases risk for poor functioning and worse clinical outcomes in young adulthood (Nijjar et al., 2016; Ostiguy et al., 2012). Thus, preventative interventions targeted toward this developmental stage are vital given their potential to reduce dysfunction and possibly prevent negative outcomes all together (Bruce et al., 2013).

Given the paucity of family-based prevention programs targeting OBD during childhood, a novel program was developed to meet the specific needs of young OBD and their families entitled *Reducing Unwanted Stress in the Home* (*RUSH*; Serravalle et al., 2021). The RUSH program, a skills-based intervention, sought to improve functioning in the home environment and provide both parents and children with stress-coping skills (Serravalle et al., 2021). By making substantiative changes to the family environment and improving stress-coping, the program aimed to reduce emotional and behavioural problems in at-risk children, thereby reducing their risk for later psychopathology. Participation in the RUSH prevention program did not directly affect offspring's internalizing symptoms relative to control children (i.e., parents did not have a mental disorder), but was associated with a decrease in externalizing symptoms post-intervention. However, these changes did not persist at the six-month follow-up in the full sample (Serravalle et al., in preparation). Participation in the RUSH program, however, was associated with long-term improvement (six-month follow-up) of internalizing and externalizing problems in OBD for those families that experienced intervention-related reductions in parental stress (Resendes et al., 2023), reductions in negativity during a parent-child interaction (Serravalle et al., 2021), and elevations in organization of the family environment (Serravalle et al., in preparation). Intervention-related changes to the family environment were also found to impact the hypothalamic-pituitary-adrenal (HPA) axis, with improved organization and cohesion associated with elevated diurnal cortisol levels over time (Yong Ping et al., in preparation). These findings suggest that the RUSH prevention program exerted its long-term positive effects on the OBD by way of improved parenting behaviours and family functioning, and that effects of the program may not be experienced equally across participating OBD. Although the findings above show how intervention-related changes in the home environment are critical to eliciting

behaviour change in high-risk children, one might also consider how individual characteristics, such as biological markers, make some children more responsive to an intervention or their environmental context than others (Belsky et al., 2007; Pluess & Belsky, 2013).

Various biological factors, including genes, hormone levels, and brain functioning, have been found to moderate how individuals respond to their environment (Glenn, 2019). Specific allelic variations of serotonin, dopamine, and oxytocin related genes have been associated with greater susceptibility to both positive and negative environments (Bakermans-Kranenburg & van Ijzendoorn, 2011; Glenn et al., 2018; van Ijzendoorn et al., 2012). A recent meta-analysis found that individuals with specific genotypes (i.e., ss or sl) on the serotonin transporter gene (5HTTLPR) were more likely to experience negative outcomes in response to adverse environments and to profit more from positive environments compared to those individuals with an alternate ll genotype (van Ijzendoorn et al., 2012). Research has also pointed to underlying stress neurobiology, specifically the HPA axis, as moderating individual susceptibility to environmental context (Bruce et al., 2013). The HPA axis plays a fundamental role in maintaining physiological homeostasis in the face of physical or psychological demand (McEwen, 2008). Diurnal cortisol levels have been found to influence children's sensitivity to adverse environmental contexts, including low family income, harsh parenting practices, parental symptoms of depression, and peer victimization on a variety of developmental outcomes, including executive function and internalizing and externalizing behaviours (Chen et al., 2015; Laurent et al., 2013; Obradovic et al., 2016; Rudolph et al., 2011; Vaillancourt et al., 2018). Interestingly, both high (Obradovic et al., 2016) and low (Vaillancourt et al., 2018) diurnal cortisol profiles have predicted poor developmental outcomes in children and adolescents in response to adverse environments.

In contrast, research examining the role of the HPA axis in moderating individuals' responsiveness to supportive and enriching environments has been limited. Most research has consisted of studies examining environments characterized by the absence of risk factors (e.g., high family income, low peer victimization). Nevertheless, variation in stress responsivity was found to influence the impact of such environments on child mental health outcomes (Obradovic et al., 2016; Rudolph et al., 2011). With respect to intervention research, van de Wiel et al. (2004) examined the moderating role of HPA axis functioning on the efficacy of an intervention in a sample of children with disruptive behaviour disorder. Children who showed high cortisol reactivity in response to a stressor demonstrated a reduction in behavioural problems following exposure to the psychotherapeutic intervention compared to children with low cortisol reactivity. Overall, further research is needed to examine the role of diurnal cortisol patterns as a marker of individual sensitivity, affecting how at-risk populations respond to their environment not only in contexts of adversity, but also in response to enrichment, such as exposure to preventative interventions (Bruce et al., 2013).

The goal of the present study was to examine whether indices of diurnal HPA function moderated the impact of the RUSH program on internalizing and externalizing behaviours in the OBD. This proof-of-concept study used a quasi-experimental design with an intervention arm for families with a parent having BD and an assessment-only arm for offspring being raised by parents with no history of affective disorder (i.e., control families). All families were followed longitudinally to examine offspring emotional and behavioural functioning up to six-months post-intervention. Three diurnal cortisol patterns were measured via saliva sampling: cortisol awakening response (CAR), total daily cortisol output, and diurnal cortisol slope. As offspring of parents with BD and major depressive disorder show elevations in diurnal and reactive cortisol

levels (Ellenbogen et al., 2010; Klimes-Dougan et al., 2022), and that elevated cortisol levels have been shown to predict later affective disorders (Ellenbogen et al., 2011), we expected elevated diurnal cortisol to identify those OBD in greatest need of the prevention program. Thus, we hypothesized that OBD with elevated CAR, greater total cortisol output, and steeper diurnal slopes would demonstrate the greatest reductions in internalizing and externalizing symptoms following participation in the RUSH program.

Methods

Participants

A total of 45 families participated in the present study. Of these, 20 families had a parent with a diagnosis of BD and participated in the *Reducing Unwanted Stress in the Home (RUSH)* preventative intervention program. Families were eligible to participate in the prevention program if one parent met diagnostic criteria for BD (type I or II) according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV; American Psychiatric Association, 2004). Families were recruited from local hospital clinics and patient support groups, as well as through online and newspaper advertisements, in Montreal (Canada) and surrounding regions. Parents who did not meet diagnostic criteria for a current axis-I disorder or a past episode of major depressive disorder according to the DSM-IV were recruited into the control group. Twenty-five control families from the same geographical region were recruited using similar advertisement methods. All participating families met eligibility criteria of having one or more biological child between 6 to 11 years of age and being fluent in either English or French. Children were excluded from participating if they met criteria for a past or present affective, psychotic, or pervasive developmental disorder, or presented with an intellectual or

chronic physical disorder. Demographic information for study participants is presented in Table 1.

Parent Mental Health Status

Parents were administered the Structured Clinical Interview for DSM-IV-R (SCID-I; First et al., 2002), a semi-structured diagnostic interview, to assess the presence of axis-I mental disorders. The SCID-I has moderate to excellent inter-rater reliability with kappa values ranging from .61 to .83 for axis I disorders (Lobbestael et al., 2011). The SCID-I was administered in English or French using the validated translation of the SCID-I.

Family socioeconomic status (SES) was computed using the Hollingshead Index criteria which drew from families maternal and/or paternal level of education and employment (Hollingshead, 1973).

Offspring Mental Health Status and Emotional and Behavioural Functioning

The Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version (K-SADS-PL; Kaufman et al., 1997) was administered to parents at recruitment to confirm the diagnosis of current and/or past episodes of psychopathology in the child.

The Parent Rating Scales-Child form (PRS-C) of the Behavior Assessment System for Children, Second Edition (BASC-2; Reynolds & Kamphaus, 2004) was administered to parents to measure their children's internalizing and externalizing behaviours. On 160 items, parents rated how frequently each behaviour occurred in their child using a four-choice response format, including 0 (never occurs), 1 (sometimes occurs), 2 (often occurs), or 3 (almost always occurs). For the present study, only the internalizing and externalizing composites were summed using their respective subscales and analyzed. The internalizing composite consisted of the anxiety, depression, and somatic complaints subscales, while the externalizing composite consisted of the

hyperactivity, aggression, and conduct problems subscales. Psychometric data pertaining to the measure demonstrate high internal consistency and test-retest reliability, with alpha coefficients on the composites and scales exceeding 0.80 (Reynolds, 2010).

Offspring Saliva Cortisol Sampling

At each phase of testing, parents were instructed to collect saliva samples from their children at six time-points across two consecutive days: awakening, 30-minutes post-awakening, 60-minutes post-awakening, 1300h, 1500h, and 2000h or bedtime. Parents were instructed to have their children refrain from eating or drinking 30 minutes prior to the collection of each sample to avoid contamination. Saliva samples were collected using passive drool into mini 6 ml polypropylene vials and with a straw if needed. In addition to parent-reported timing of saliva collection, vials were stored in larger vials that utilized time-stamping micro-circuity within the cap. Such circuitry automatically recorded the times at which the cap was opened and closed. Both parent-report and time-stamping recordings were used to obtain a measure of sampling compliance. Following collection, parents were instructed to place the samples in their freezer until pickup was arranged. Samples were then stored in a -20°C freezer at Concordia University. Samples were assayed at the Douglas Mental Health University Institute in duplicate using a sensitive commercial enzyme immunoassay kit from Salimetrics (State College, Pennsylvania). Across all phases of testing, the intra- and inter-assay coefficients of variability were 4.80% and 6.99%, respectively, and the sensitivity of the assay was set at 0.012 µg/dl.

To correct for positive skew, cortisol values were transformed using a natural log transformation. All outlier cortisol values were winsorized to three standard deviations from the mean. Three patterns of diurnal cortisol secretion were measured to examine different facets of circadian regulation of the HPA axis. The cortisol response following awakening (CAR) was

computed from the first three morning cortisol samples utilizing the area under the curve with respect to increase formula (AUCi; Pruessner et al., 2003). CAR measures the marked elevation in cortisol following morning awakening, and is believed to capture both reactive and circadian regulatory aspects of the HPA axis, given that it follows the action of awakening and occurs roughly at the same time every 24 hours (Stalder et al., 2016). Next, total daily cortisol output was computed using all cortisol values across the day with the area under the curve with respect to ground formula (AUCg; Pruessner et al., 2003). Finally, diurnal cortisol slope was computed by calculating the rate of change in cortisol from peak morning (30-minutes post-awakening) to evening levels (2000h; Adam et al., 2017). Computed patterns of diurnal cortisol secretion were averaged across the two days of cortisol sampling at each phase to reduce intra-individual variability, thereby increasing reliability of estimated cortisol secretory patterns.

To control for variability in timing of saliva collection, the total amount of time (in minutes) that participants' saliva sampling deviated from the designated collection time (e.g., 1300h, 1500h, and 2000h) was summed to create a measure of compliance for each sampling time. This value was averaged over the two days of sampling and the number of phases completed.

RUSH Prevention Program

The RUSH prevention program was a 12-week, manual-based preventative intervention that aimed to improve the family environment and individual stress-coping abilities. Separate parent and child sessions were conducted concurrently in weekly closed groups. Parent sessions provided psychoeducation about stress and stress-coping, and covered three primary modules including problem-solving, communication, and organization and discipline. Child sessions focused on coping strategies to manage stress, including thought restructuring, problem-solving,

emotion labeling, relaxation, and assertiveness training. This prevention program drew from previously validated family-based and stress management interventions, in order to improve organization and consistency in the home, parenting practices, family relationships, and stress coping (Abramowitz, 2012; Kendall & Hedtke, 2006; Miklowitz, 2010). For detailed information about the RUSH prevention program, see Serravalle et al. (in preparation)

Procedure

Families interested in participating in the present study were invited to undergo a brief telephone interview to screen for initial eligibility. All families meeting eligibility criteria were then invited to the laboratory to undergo diagnostic assessments in parents and children. Parents who met diagnostic criteria for BD I or II were invited to participate in the RUSH prevention program that lasted three months. Parents who did not meet criteria for a past or present axis I diagnosis were assigned to the control group. All families were invited to participate in four assessment phases: baseline (prior to the onset of RUSH), post-prevention, and 3- and 6-months post-prevention. At each assessment phase, families completed a comprehensive assessment and were provided with collection materials for saliva sampling. For the present study, only data pertaining to children's internalizing and externalizing behaviours (BASC-2) and salivary cortisol values were examined. Voluntary informed consent and assent from the parents and children, respectively, were collected at the onset of testing. Following the completion of each phase of testing, parents were compensated between $80 to $100 depending on the phase of the study, and children were given a small toy. All phases of the study were approved by the Human Research Ethic Committee of Concordia University (Montreal, Canada).

Statistical Analyses

The mean, standard deviation, range, and/or percentage of the predictor, outcome, and control variables were computed for both the OBD and control participants (see Table 1). Control variables in the present study included child age at baseline, family socioeconomic status (SES), and time variability of cortisol sampling.

Hierarchical Linear Modeling 6.0 (HLM 6.0; Raudenbush, 2004) was used to compute growth curve models estimating whether baseline HPA axis functioning predicted changes in offspring internalizing and externalizing behaviours over the course of the study. At Level 1, we estimated the variance in offspring's internalizing or externalizing behaviours across the four phases of testing as a function of an intercept, uncentered scores of time, and a residual term. Given that the intercept was entered uncentered, it represented the offspring's behavioural outcome at baseline. The coefficient of primary interest was the estimation of the slope (time), which examined changes in offspring internalizing or externalizing behaviours across time. At Level 2, the baseline measure of HPA axis functioning was entered as a predictor of intercept and slope. Due to constraints of power, only covariates that significantly predicted the outcome of interest were included in the final model. Separate models were computed for each index of baseline HPA axis functioning, including CAR, daily total cortisol output, and diurnal cortisol slope. To illustrate the significant main effects on the time slope, we applied the recommended growth-curve techniques (Preacher et al., 2006), estimating internalizing and externalizing behaviours across time as a function of baseline HPA axis functioning (mean, one standard deviation above and below the mean). Similar HLM modelling was conducted with the control participants to determine whether effects observed in the OBD were specific to the at-risk group and, thus, attributable to the RUSH prevention program.

All Level 2 predictor variables were standardized prior to conducting the analyses. The reported effects are based on models using restricted maximum likelihood estimation and robust standard errors.

Results

Preliminary Analyses

Means, standard deviations, and frequencies or ranges of predictor, outcome, and control variables for both the OBD and the healthy controls are reported in Table 1. Paired samples t-tests indicated that externalizing behaviours at phase 1 were significantly greater in the OBD than the healthy controls, $t(53) = -2.15$, $p = .036$. In addition, OBD were also found to be significantly younger than control offspring, $t(53) = 2.35$, $p = .02$. Zero-order Pearson correlations between the main study variables in the OBD are presented in Table 2.

Predicting change in offspring internalizing behaviours

HLM analyses were conducted to estimate the effects of baseline diurnal cortisol on internalizing behaviours in the OBD in response to the RUSH prevention program, as presented in Table 3. The Level 1 model found a significant effect for the intercept, indicating that participants' internalizing behaviours at baseline were significantly different from zero ($p < .001$). Internalizing behaviour on the time slope was not significant, suggesting that symptoms were relatively stable across time in the entire sample. Finally, results from the Level 1 model showed that there was significant variance around participants' average intercept $\chi^2 = 144.90$, $df = 25$, $p < .001$, and slope (time), $\chi^2 = 44.01$, $df = 25$, $p < .01$. Given the significant variance around both intercept and slope, analyses proceeded to Level 2.

In the Level 2 model, we predicted the observed variance in the intercept and slope of participants' internalizing behaviours as a function of the baseline diurnal cortisol marker and

those covariates that were significant (see Table 3). For the first model including CAR, no significant effects were found for the predictor or covariates at the intercept (baseline). For the prediction of slope, baseline CAR predicted a change in internalizing behaviours over time (coefficient = 0.36, *SE* = 0.12, *T-ratio* = 3.15, $p < .01$). The final model accounted for 9.76% of the variance in internalizing behaviours over time. Follow-up analyses of the simple slopes (see Figure 1a) found that low CAR at baseline predicting a significant decline in internalizing behaviours across the duration of the study (coefficient = -0.63, *SE* = .24, *T-ratio* = -2.68, $p < .05$). In contrast, no significant changes in internalizing behaviours across time were observed in those OBD with mean (coefficient = -0.27, *SE* = .20, *T-ratio* = -1.34, *ns*) and high baseline CAR values (coefficient = 0.10, *SE* = .23, *T-ratio* = 0.44, *ns*).

With respect to total cortisol output, no significant effects were found for the predictor or covariates at the intercept. For the slope, baseline total cortisol output was found to significantly predict internalizing symptoms (coefficient = 0.51, *SE* = 0.24, *T-ratio* = 2.15, $p < .05$). Simple slope analyses (see Figure 1b) revealed low total cortisol levels at baseline predicted declining internalizing behaviours across time (coefficient = -0.77, *SE* = .23, *T-ratio* = -3.40, $p < .01$). In contrast, no significant changes in internalizing behaviours were observed for OBD with mean (coefficient = -0.26, *SE* = .19, *T-ratio* = -1.38, *ns*) or high total cortisol output (coefficient = 0.25, *SE* = .37, *T-ratio* = 0.67, *ns*) at baseline. After controlling for SES, total cortisol output explained 25.34% of the variance in internalizing behaviours over time.

Finally, with respect to diurnal cortisol slope, no significant effects were found at the intercept. There was a significant effect of diurnal cortisol slope on the slope, such that baseline diurnal slope predicted internalizing behaviours over time (coefficient = -0.45, *SE* = 0.11, *T-ratio* = -3.93, $p < .01$). The final model accounted for 11.43% of the variance. Follow-up simple slope

analyses (see Figure 1c) found that OBD with flatter diurnal cortisol slopes at baseline exhibited a significant decline in internalizing behaviours across time (coefficient = -0.69, *SE* = 0.23, *T-ratio* = -3.06, $p < .01$). In contrast, no significant changes in internalizing behaviours were evident over time in those OBD with mean (coefficient = -0.24, *SE* = .20, *T-ratio* = -1.22, *ns*) and steeper diurnal cortisol slopes (coefficient = 0.21, *SE* = .23, *T-ratio* = 0.91, *ns*) at baseline

Given the observed differences in internalizing symptoms at time 1 between individuals with low, mean, and high baseline diurnal cortisol levels, the analyses were repeated controlling for baseline internalizing behaviours in addition to SES. Baseline cortisol awakening response ($p < .05$) and diurnal slope ($p < .01$) remained significant predictors of internalizing symptoms over time, while total cortisol output became marginally significant ($p = .07$; see Appendix A).

Predicting change in offspring externalizing behaviours

Similar HLM models were computed to estimate offspring externalizing behaviours from baseline markers of HPA axis functioning and covariates. The Level 1 model found a significant effect for the intercept, indicating that participants' externalizing behaviours at baseline were significantly different from zero ($p < .001$). Externalizing behaviours along the slope (time) were not significant, indicating that externalizing behaviours were stable across time for all OBD. Finally, results from the Level 1 model found significant variance around participants' externalizing behaviours at the intercept, $\chi^2 = 314.73$, $df = 25$, $p < .001$, and along the slope (time), $\chi^2 = 94.84$, $df = 25$, $p < .001$. As such, analyses proceeded to Level 2.

With respect to the Level 2 models, no significant main effects of baseline diurnal cortisol indices were found at either the intercept or across the slope (see Appendix B).

Predicting change in internalizing and externalizing behaviours in healthy controls

Similar analyses were conducted for the healthy control offspring, estimating effects of baseline diurnal cortisol on internalizing and externalizing behaviours over time. No significant effects were found (see Appendix C).

Discussion

The present study assessed whether indices of HPA axis function prior to participating in a preventative intervention predicted the OBD's response to the intervention. We predicted that offspring with high cortisol levels and a steep diurnal cortisol slope at baseline might benefit the most from the RUSH prevention program compared to those who had low levels of cortisol and a flatter slope. The hypothesis was supported in part, in that that HPA function at baseline predicted response to the intervention. However, the direction of the relationship was reversed. OBD with lower CAR and total daily cortisol output, as well as flatter diurnal cortisol slopes at baseline exhibited a significant decline in their internalizing symptoms in response to the RUSH program. The findings even persisted after controlling for pre-intervention levels of internalizing symptoms in children. Conversely, OBD with elevated baseline CAR and total cortisol output, and steeper diurnal cortisol slopes exhibited no significant change in internalizing behaviours across time in response to the RUSH program. No significant effects were found for externalizing behaviours. In addition, these findings were not replicated in the control offspring who did not participate in the RUSH program but underwent all assessments.

Results from the present study suggest that diurnal cortisol levels predict OBD's sensitivity to environmental change, particularly in the context of enrichment. Contrary to our hypotheses, children with attenuated diurnal cortisol patterns, not elevated ones, garnered the greatest benefits from the RUSH program. Our hypotheses were based on previous studies demonstrating high cortisol levels in OBD (Ellenbogen et al., 2006; Ellenbogen et al., 2010). It is

important to highlight that this research was based on adolescent samples. Findings in children have often demonstrated blunted cortisol levels to be associated with exposure to early-life adversity (Kliewer et al., 2019; Ouellet-Morin et al., 2011; Yong Ping et al., in preparation). Furthermore, extensive research has linked flatter or dampened cortisol slope with generally worse physical and mental health outcomes in both normative and at-risk populations (Adam et al., 2017; Cicchetti et al., 2010; Ouellet-Morin et al., 2011). With respect to CAR and daily levels, lower cortisol levels have been typically associated with externalizing problems and, to a lesser degree, internalizing behaviours (Badanes et al., 2011; Loney et al., 2006). Thus, contrary to our predictions, lower cortisol during childhood may function to identify those OBD at greatest risk for adverse outcomes and thus in greatest need of prevention. To date, only one study has examined the HPA axis as a marker of treatment responsivity, finding that high cortisol reactivity in response to a stressor was associated with a decrease in externalizing behaviours post-intervention (van de Wiel et al., 2004). As cortisol levels in response to a psychosocial stressor do not correlate with diurnal cortisol levels (Kidd et al., 2014), and Van de Wiel et al (2004) studied children with disruptive behaviour disorders, results across studies were not comparable.

The present study is the first of its kind to provide evidence that *diurnal* cortisol levels may function as a neuroendocrine marker of sensitivity to family-based interventions and/or positive changes in the environment. The present findings do align with past studies that have examined indices of the autonomic nervous system, including baseline respiratory sinus arrhythmia (RSA) that is indicative of parasympathetic nervous system (PNS) functioning. (Khurshid et al., 2019). RSA activity has been found to moderate the impacts of the family environment on internalizing outcomes in youth. In particular, Khurshid et al. (2019) found that

low baseline RSA influenced the impact of marital conflict on adolescent internalizing behaviours in both a positive and negative direction. Lower marital conflict, thought to represent an improved family environment, was associated with lower internalizing behaviours in adolescents with low baseline RSA. Lower baseline RSA was suggested to reflect a low threshold for activation of the autonomic nervous system, potentially facilitating system activation and greater sensitivity in response to positive family environments (Khurshid et al., 2019). Thus, lower baseline RSA and HPA axis functioning may be associated with increased sensitivity of these systems to environmental change via early intervention. Evidence that the two systems work in parallel also comes from findings that low RSA in conjunction with low baseline cortisol have been associated with lower levels of depression symptoms in school-aged children (El-Sheikh et al., 2011).

Overall, the results from the present study suggest that diurnal cortisol patterns influence how individuals respond to positive and promotive environments. Such results lend support to the *vantage sensitivity* hypothesis that endogenous factors are associated with individual variability/sensitivity to positive influences (Pluess & Belsky, 2013). Our results suggest that attenuated HPA axis functioning, evidenced by decreased CAR, total cortisol output, and flatter diurnal cortisol slope, may identify those individuals most likely to benefit from positive environments in the form of improved family functioning and stress-coping capabilities. Conversely, elevated diurnal regulation of the HPA axis may confer *vantage resistance*, identifying those individuals who are less likely to benefit from positive influences within their environment and, thus, less likely to exhibit changes in their behaviours.

Evidence from the present study highlights that biomarkers, such as the HPA axis, may prove worthwhile in identifying those individuals most likely to benefit from preventative

interventions (Glenn, 2019). Such markers may also function to identify individuals least likely to respond to a preventative intervention, perhaps as a form of resiliency to both negative and positive environments. Given the substantial costs associated with prevention programs, information about individual sensitivity could be used to aid in the tailoring of interventions to meet the specific needs of the children being targeted. In other words, identification of biomarkers that differentiate intervention responders versus non-responders could prove worthwhile in identify what works for whom (Belsky & van Ijzendoorn, 2015). Tailoring interventions based on individual sensitivity factors could allow for adjustments in how an intervention is administered; intensity (e.g., increased frequency of sessions) and duration (e.g., increased length of sessions) could be adjusted depending on an individual's predetermined level of risk. Such an approach to intervention administration could reduce overall financial costs and burden associated with the implementation of large-scale prevention programs and increase programs' efficacy in reducing negative outcomes in at-risk populations, such as the OBD.

There are several limitations to the present study. First, the sample size was small, limiting statistical power. However, the study included four time points and used multilevel modelling with restricted maximum likelihood estimation to minimize this limitation. Second, the present study did not utilize a randomized controlled trial design - the gold standard in intervention research. In this proof-of-concept project, there was no control group of at-risk OBD who did not participate in the RUSH program or participated in a comparison intervention. The inclusion of such a group, and thus an RCT design, would have required resources beyond the scope of the current pilot project. Third, children recruited into the present study were primarily white and from middle class families, which limits the generalizability of the present findings to other diverse groups. Future research would benefit from using a larger sample of OBD that

would allow for the randomized assignment of OBD to either the RUSH prevention program or a waitlist control/care-as-usual or psychoeducation group. In addition, future research would also benefit from continued longitudinal follow-up of high-risk youth undergoing the RUSH protocol into adolescence and adulthood. Such a longitudinal design would elucidate whether the benefits of the RUSH prevention program, in tandem with baseline HPA axis functioning, extended from childhood and into adolescence. If results were found to persist longitudinally, this would speak to the long-term benefits of RUSH as an effective prevention for diminishing or preventing the later development of mental health symptoms.

Despite these limitations, the present study is the first of its kind to examine how diurnal cortisol levels predict OBD's sensitivity to RUSH, a novel family-based prevention program. The present results highlight the pertinent role of diurnal cortisol in differentiating those OBD most likely to respond to preventative interventions from those who do not. Such findings will hopefully inform future preventative intervention research that aims to further elucidate the role of biomarkers in predicting individual sensitivity to promotive and supportive environments.

Table 1. Means, Standard deviations, Range, and Frequencies of study variables (N=55).

Variables	Mean (SD) or Frequency count (%); Range	
	OBD Group	Control Group
Intervention Group	26 (47.3%)	29 (52.7%)
Internalizing		
Phase 1	25.12 (10.01)	21.48 (11.14)
Phase 2	22.77 (12.36)	19.10 (10.34)
Phase 3	23.31 (13.51)	19.62 (11.53)
Phase 4	21.75 (11.36)	17.69 (11.03)
Externalizing		
Phase 1	19.46 (11.69)	13.76 (7.74)
Phase 2	17.58 (11.11)	15.28 (8.05)
Phase 3	17.62 (10.32)	14.62 (8.10)
Phase 4	18.40 (11.25)	13.83 (7.83)
Cortisol (P1)		
CAR increase	-0.20 (2.36)	-0.27 (2.85)
AUC ground	39.55 (23.86)	40.77 (20.80)
Diurnal slope	-0.01 (.01)	-0.01 (.01)
Age in Months (P1)	93.92 (22.03); 69-142	106.97 (19.11); 73-150
Socioeconomic status (SES)	9.23 (2.34); 5-12	9.69 (1.29); 7-12
Sex (female)	12 (46.2%)	17 (58.6%)
Ethnicity		
White	39 (70.9%)	
Indigenous	2 (3.6%)	
Black	5 (9.1%)	
East Asian	1 (1.8%)	
Hispanic/Latino/Latin-American	4 (7.3%)	
Middle Eastern/North African/ Central Asian	4 (7.3%)	

Notes. P = phase. CAR = cortisol awakening response. AUC = area under the curve. OBD = offspring of parents with bipolar disorder. SES – higher value indicates higher SES.
* $p < .05$; ** $p < .01$.

Table 2. Zero-order Pearson Correlations of main study variables in the OBD (N=26).

	1	2	3	4	5	6	7	8
1. Internalizing (P1)								
2. Externalizing (P1)	.027							
3. CAR AUCi (P1)	-.209	.002						
4. AUCg (P1)	-.262	-.072	.531**					
5. Slope (P1)	.181	-.140	-.650***	-.775**				
6. Age (P1)	.066	-.071	.321	.246	.335			
7. Sex	.162	-.105	.103	-.170	.166	.075		
8. SES (P1)	.112	.204	.265	.397*	-.468*	-.306	-.060	
9. Compliance	-.114	-.236	.074	.336	.186	-.059	-.097	.030

Notes. CAR – cortisol awakening response. AUCi – area under the curve with respect to increase. AUCg – area under the curve with respect to ground. P – phase. SES – socioeconomic status. Compliance based on collection of samples for diurnal slope.
* $p < .05$; ** $p < .01$.

Table 3. Effects of baseline diurnal cortisol levels on OBD internalizing behaviours.

	a) CAR				b) Total Cortisol Output				c) Diurnal Cortisol Slope			
	Intercept (Baseline)		Slope (Time)		Intercept (Baseline)		Slope (Time)		Intercept (Baseline)		Slope (Time)	
	Coefficient (SE)	T-Ratio	Coefficient (SE)	T-Ratio	Coefficient (SE)	T-Ratio	Coefficient (SE)	T-Ratio	Coefficient (SE)	T-Ratio	Coefficient (SE)	T-Ratio
Level 1 (β_0; β_1)	24.57 (2.00)	12.26***	-0.27 (0.21)	-1.28	24.57 (2.00)	12.26***	-0.27 (0.21)	-1.28	24.57 (2.00)	12.26***	-0.27 (0.21)	-1.28
Level 2: Main effects												
Intercept	24.57 (1.97)	12.45***	-0.27 (0.20)	-1.34	24.56 (1.87)	13.12***	-0.26 (0.19)	-1.38	24.52 (1.93)***	12.67***	-0.24 (0.20)	-1.22
Cortisol (P1)	-1.59 (2.21)	-0.72	0.36 (0.12)	3.15**	-3.95 (2.17)	-1.82	0.51 (0.24)	2.15*	2.82 (2.36)	1.20	-0.45 (0.11)	-3.93**
SES	1.36 (1.86)	0.73	-0.31 (0.12)	-2.59*	2.57 (1.66)	1.55	-0.45 (0.18)	-2.53*	2.26 (2.00)	1.13	-0.43 (0.11)	-3.74**

Notes. CAR – cortisol awakening response. AUC – area under the curve. P1 – phase 1. SES – socioeconomic status. SE - standard error.

* $p < .05$; ** $p < .01$; ***$p < .001$.

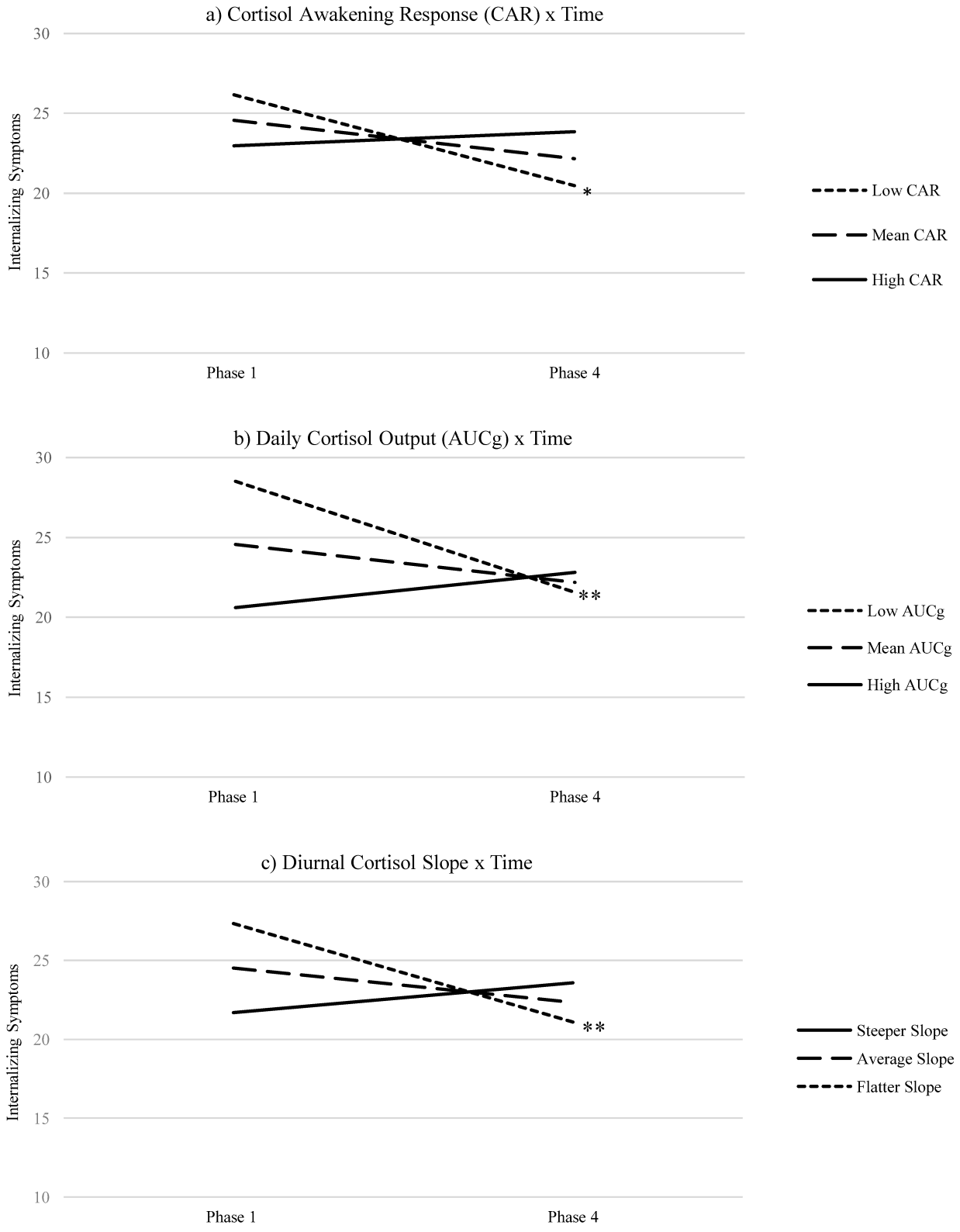

Figure 1. Internalizing behaviours over time in offspring of parents with bipolar disorder as a function of baseline a) cortisol response to awakening (CAR), b) daily cortisol output (area under the curve with respect to ground; AUCg), and c) diurnal cortisol slope. * $p < .05$, ** $p < .01$.

Chapter 5: General Discussion

Bipolar disorder (BD) is a pervasive and debilitating mental illness (Kessler et al., 2007), associated with negative outcomes in the affected individual and their family members (Crump et al., 2013). It is also the source of substantial societal burden and alarming economic costs (Chisholm et al., 2005; Magliano et al., 2009). Given far-reaching impacts of the disorder, BD prevention and early intervention has grown in priority (Benarous et al., 2016), along with the need to better understand biopsychosocial factors that increase risk and alternatively promote resiliency against adverse outcomes (Stapp et al., 2020). Advancements in the field have since been used for knowledge translation purposes, informing the development and implementation of intervention programs, and identifying those individuals at greatest risk and thus in greatest need. Offspring of parents with bipolar disorder (OBD) are a particularly vulnerable population, due to their elevated risk for developing affective disorders, including BD (Duffy et al., 2019), and other adverse outcomes (Birmaher et al., 2009; Mesman et al., 2013; Nijjar et al., 2016). Such outcomes have been attributed to their elevated genetic risk (Craddock & Sklar, 2013), as well as their increased risk for exposure to early-life environmental stressors, including but not limited to elevated family dysfunction, ineffective parenting practices, elevated martial distress, and negative stressful life events (Menculini et al., 2020; Stapp et al., 2020). Exposure to such early-life stressors is believed to become 'biologically embedded' or ingrained in biological systems, increasing risk for poorer long-term outcomes, including psychopathology (Berens et al., 2017). For these reasons, OBD have been the focus of increasing selective and indicated intervention.

Given the growing importance of prevention programs for youth at risk for BD (Post et al., 2020), study 1 of this dissertation was a systematic review that examined the efficacy of BD preventive interventions implemented over the past three decades. The review focused on studies

targeting youth (i.e., children, adolescents, and young adults) at-risk of developing BD, by way of elevated genetic risk (i.e., family member with BD) and/or identified as being in the early prodrome phase (i.e., diagnosed with BD-NOS, CYC, etc.). Generally, positive outcomes were reported across studies, including reduced affective and anxiety symptoms, reduced externalizing problems, and improved course of the disorder (i.e., rapid recovery from initial mood episode, longer 'well' period, lower conversion rate to BD). Some studies also reported improvements to the parent-child relationship, as well as parent well-being (i.e., reduced stress and increased confidence). While results from the review were generally promising, some programs failed to produce significant effects on mental health outcomes, while others had difficulty replicating results from open trials to more sophisticated randomized controlled trials. The review also identified a growing number of biopsychosocial mediating factors that explained, in part, how prevention programs function to improve outcomes in youth. Psychosocial variables relating to the individual and their environment included mindfulness, therapeutic alliance between youth and clinicians, parental expressed emotion, perceived parent-child conflict, and family psychosocial functioning. Biological variables included brain activation, connectivity, and functional and morphological network integration.

With increasing evidence to attest to the benefits of preventive interventions for at-risk youth (Perich & Mitchell, 2019), the dissertation attempted to determine whether prevention programs might elicit effects 'under the skin' in youth at risk for BD. Study 2 of this dissertation examined the effects of a family-based prevention program, entitled Reducing Unwanted Stress in the Home (RUSH), on hypothalamic-pituitary-adrenal (HPA) axis function in a sample of OBD from baseline up to 6-month post-intervention. Diurnal HPA axis function in OBD was compared to that of healthy controls who underwent assessments but did not participate in the

prevention. Contrary to our hypotheses, no differences were found in diurnal cortisol between OBD and healthy controls. However, to the family environment, specifically increased organization and cohesion, were associated with significant increases to diurnal cortisol levels over time in OBD, including increased cortisol awakening response and daily cortisol output, as well as a steepening of the diurnal cortisol slope.

The final study of this dissertation aimed to assess a novel hypothesis that has been explored in other areas of research: whether traits or characteristics of youth can be used to predict a stronger response to a prevention program (Hankin, 2020). Study 3 examined whether diurnal cortisol levels predict OBD response to the RUSH program. Baseline diurnal cortisol, including lower cortisol awakening response and total output, and flattened diurnal slope, were associated with significant declines in internalizing symptoms following the RUSH program up to 6-months post-intervention.

The Role of the HPA axis in Offspring of Parents with Bipolar Disorder (OBD)

This dissertation aimed to further elucidate the role of the HPA axis in predicting risk and resiliency in OBD. Diurnal cortisol was measured in OBD, first as a biomarker of risk, second to examine sensitivity of HPA axis function to contexts of risk and resiliency, and third as a biomarker differentiating how individuals respond to preventive interventions.

HPA axis as a biomarker of risk

For decades, researchers have sought to understand the biological underpinnings of disease, with interests extending from physical to mental illness. Biomarkers, or biological antecedents, are defined as objective indicators that can be accurately measured and used to predict clinical outcomes (Strimbu & Tavel, 2010). Interest in identifying biomarkers of psychopathology has grown largely from an impetus to improve identification of those at

greatest risk and in greatest need of selective or indicated prevention (Bruce et al., 2013; Nemeroff & Vale, 2005).

With respect to affective disorders, researchers have focused heavily on the HPA axis, stemming from the direct and linear relationship between stress and disease for both physiological and psychological outcomes (Cohen et al., 2007; Hammen, 2005). Evidence of hyperactivity of the HPA axis, such as the presence of elevated cortisol levels, has become one of the most robust and reliable findings when comparing depressed adults to healthy populations (Ehlert et al., 2001; Nemeroff & Vale, 2005; Zorn et al., 2017). It has been reported that anywhere from 20 to 80 percent of depressed individuals exhibit HPA axis hyperactivation in the form of elevated cortisol levels across the day, increased frequency of cortisol secretion episodes, and elevated magnitude of cortisol secretion with each pulse (Guerry & Hastings, 2011; Stetler & Miller, 2011). In addition to cross-sectional research findings, longitudinal studies have identified elevated cortisol levels as a potential predictor of major depressive disorder (Kennis et al., 2020).

Similar findings, however, are not as readily observed in pediatric samples. Lopez-Duran et al. (2009) conducted a meta-analysis of research studies examining basal cortisol levels across the day in depressed and non-depressed youth. Children and adolescents with depression exhibited moderately elevated basal cortisol levels across the day compared to non-depressed controls. However, findings have not been consistent. Guerry and Hastings (2011) updated the work of their predecessors but failed to find significant differences between depressed and non-depressed youth on numerous indices of basal HPA axis functioning.

To determine the HPA axis' role as a biological marker of risk, research has extended to examining its functioning in samples at-risk for affective disorders. Adolescent and adult

offspring of parents with affective disorders have been found to demonstrate elevations in diurnal (morning and afternoon) and reactive cortisol levels (Ellenbogen et al., 2010; Klimes-Dougan et al., 2022). However, results from the present dissertation (study 2) in children were inconsistent with these findings. Indices of baseline diurnal cortisol, including the cortisol response following awakening, total daily output, and diurnal slope, did not significantly differ between children whose parents had BD and those whose did not. These findings were unexpected given that OBD typically evidence greater early life adversity, which has been linked to neuroendocrine stress dysregulation (Raymond et al., 2018).

The lack of significant group differences may be attributable to the study's small sample size, which limited statistical power, and the relatively young age of the sample compared to past studies (Goldstein et al., 2018; Leopold et al., 2020; Miklowitz, Schneck, et al., 2020). The sample's young age may have limited the chronicity of early-life stress exposure and subsequently the impact of stress on the development and functioning of the HPA axis. The lack of significant findings may have also stemmed from the sample's assumed early stage of pubertal development. Patterns of cortisol secretion in dysphoric youth have typically been dependent on the stage of pubertal development, with hypersecretion typically evident during adolescence when circulating sex hormones are presumed to be high (Hankin et al., 2010). Similarly, pubertal stage has been found to impact the effect of early stress exposure on the cortisol awakening response. Early-life stress was associated with blunted CAR for those individuals in earlier stages of puberty, while those in later stages demonstrated a positive association between CAR and early-life stress (King et al., 2017). Overall, the inability to uncover significant differences in cortisol markers in study 2 may be attributable to the age of the study sample (6 to 11 years of age) and their presumed prepubertal stage of development.

Sensitivity of the HPA axis to contexts of risk and resiliency

Decades of research focusing on the HPA axis, and associated cortisol levels, have produced considerable evidence attesting to the effects of early-life stress exposure on brain development, evident through altered HPA axis functioning across the lifespan (Lupien et al., 2009). Exposure to stress during critical periods of brain development, including prenatal and postnatal periods, as well as adolescence, have been associated with elevated (Glover et al., 2010; Gutteling et al., 2005) and blunted (O'Connor et al., 2013) basal cortisol, as well as elevated (Yong Ping et al., 2015; Yong Ping et al., 2020) and dampened (Gunnar et al., 2009; O'Connor et al., 2013) cortisol reactivity in response to stressors (e.g., separation-reunion paradigms, Trier Social Stress Test). Furthermore, such impacts on the HPA axis have been associated with negative outcomes in childhood and adolescence, including depressive symptoms (Halligan et al., 2007; Van den Bergh et al., 2008), behavioural problems (Alink et al., 2008), and cognitive impairments (Raymond et al., 2018).

Given the sensitivity of the HPA axis to early-life stressors, the present dissertation examined how early interventions during critical stages of development may impact the HPA axis. In other words, study 2 examined whether the HPA axis would show plasticity and change in response to a preventive intervention that aimed to improve the family environment. Results from study 2 found that cortisol levels in OBD did not differ from that of healthy controls in response to the RUSH prevention. These results were unexpected, as past studies have reported efficacy of preventive interventions altering indices of HPA axis functioning (Fisher et al., 2007; Fisher et al., 2011). Upon closer inspection, study 2 found that OBD whose environment demonstrated improvements to family organization and/or cohesion following RUSH, did indeed exhibit significant changes to their HPA axis functioning. Increased organization and cohesion

scores following RUSH were associated with elevations in the cortisol awakening response and total daily cortisol output, as well as a steepening of diurnal cortisol slope, across time. The findings add to the small body of literature demonstrating that positive environmental influences, in the form of psychosocial interventions, can induce changes to the HPA axis in children (Slopen et al., 2014), particularly in those whose families experience concurrent improvements in known risk factors (e.g., improved family functioning). Collectively these findings suggest continued plasticity of the HPA axis into childhood, which allows for possible 'repair' with timely and effective preventive interventions. These findings have important clinical implications. As dysregulated HPA axis functioning has been speculated to underlie affective disorders (Ellenbogen et al., 2011), altered or 'repaired' HPA axis functioning may constitute a change for the better, improving mental health outcomes in the long-term.

The HPA axis as a marker of individual susceptibility to prevention

Universal prevention, while rooted in an ideal to improve outcomes for all, comes at significant economic costs. Their utility has also been called into question given their typically 'modest' treatment effects (Albert et al., 2015). As such, selective preventions that aim to target populations at greatest risk, as well as individuals increasingly susceptible to intervention, provides an increasingly effective and efficient approach to helping those in need. The concept of differential susceptibility stipulates that underlying factors, such as biomarkers, function to influence how individuals respond to their environment for better and for worse (Belsky et al., 2007). The "bright side" of the differential susceptibility hypothesis, also referred to as the vantage sensitivity hypothesis (Pluess & Belsky, 2013), suggests that individuals possessing specific biological factors will be more likely to garner positive effects when placed in positive or promotive environments, including prevention programs that function to ameliorate known

risk factors (Glenn, 2019). Stress neurobiology has been implicated in this hypothesis and thought to impact how individuals respond to preventive interventions (Bruce et al., 2013). As such, study 3 of this dissertation aimed to examine the role of diurnal cortisol as a biological factor conferring advantage to those exposed to the RUSH program.

Results from study 3 of the dissertation found HPA axis function prior to the intervention identified those children most sensitive to the positive effects of the RUSH program. Specifically, participation in RUSH predicted a decline in internalizing symptoms among those youth who exhibited dampened cortisol awakening responses and flattened diurnal cortisol slope at baseline. Conversely, no change in internalizing symptoms was observed for children in the RUSH program without these indices of HPA function prior to the intervention. The findings are in line with previous research where gene variants and reactivity of the HPA axis influenced how individuals responded to their environment, particularly in contexts of advantage (Eley et al., 2012; van de Wiel et al., 2004). Moreover, these results contribute to a growing discussion on how biological factors, such as HPA axis regulation, can be used to inform future prevention efforts. Such knowledge may be used to adapt programming (i.e., frequency, duration, and intensity) in an attempt to bolster prevention efforts (Belsky & van Ijzendoorn, 2015).

Limitations

Several limitations in the dissertation should be highlighted. With respect to study 1, there was much heterogeneity between identified studies. Differences pertained to the definition of 'at risk', the target of the prevention (i.e., parent and/or child), the methodological design (e.g., RCT, quasi experiment, or open trial), outcome variable(s) measured (i.e., mental health, psychosocial, familial, etc.), and the length of follow-up (i.e., pre-/post-, up to 4-years post-intervention). These differences made it particularly challenging to make direct comparisons

across studies or to draw conclusions about best practice. In addition, some of the preventive interventions included in the review have not yet been assessed using an RCT design, the gold-standard for measuring program efficacy. Less methodologically rigorous research designs call into question the reliability of the associated research findings. While results from the review were generally positive, caution should be used when interpreting the findings.

The RUSH program has several limitations, potentially limiting the strength and generalizability of findings from studies 2 and 3. First, due to limited resources, the RUSH study consisted of a small sample size, which impacted the statistical power to detect significant group differences between OBD and healthy controls. The sample size also increased the risk for type I error, resulting in possible spurious findings. Second, the study used a quasi-experimental design that included a comparison of healthy controls rather than a control group of OBD randomly assigned to a waitlist control, control intervention, care as usual, etc. Finally, the study consisted of a relatively homogenous sample of white, French-speaking, middle class participants in and around the Montreal region of Quebec. The lack of diversity in the sample may limit the generalizability of the research findings to other demographics. Collectively, these limitations emphasize the need for future replication studies using larger RCT designs.

Clinical Implications for Future Prevention and Early Intervention

As previously discussed, BD and affective disorders in general can pose severe consequences. As a result, prevention of mental illness has grown in priority, particularly with increasing evidence to attest to their cost-effectiveness or cost savings (Le et al., 2021). In general, indicated or selective prevention for depression and anxiety that focus on high-risk groups or those with subthreshold clinical presentations, have been found to be cost effective or to demonstrate good value-for-money (Le et al., 2021; Mihalopoulos & Chatterton, 2015).

Furthermore, economic evaluations of prevention programs focused on early childhood have demonstrated particularly favourable results (Zechmeister et al., 2008). Results from study 1 highlighted generally positive outcomes associated with technology-enhanced interventions requiring relatively minimal costs to implement. Jones et al. (2017) found a web-based prevention program that focused on improving parenting practices and emotion regulation to be associated with improvements in child behaviour problems and parent confidence. The web-based design required little investment in the form of 'manpower', as the modules were self-guided. Furthermore, the delivery format increased the scope of outreach, targeting individuals who might not otherwise be able to attend in-person interventions due to geographical restrictions or stigma assigned to mental illness or help-seeking behaviours.

Interventions relatively short in duration and frequency were also observed to be associated with positive outcomes. Besenek (2020) found a psychoeducation interview, lasting approximately 30 minutes in duration, to be associated with some improvements in manic and somatic symptoms compared to at-risk OBD who did not receive the intervention. Similarly, Wirehag Nordh et al. (2023) found a brief two-session intervention (Let's Talk about the Children) to be effective at preventing an increase in child mental health problems, as well as enhancing perceived parental control. Overall, these findings demonstrate a potential high return on investment for programs requiring minimal investment, by way of their short duration and low implementation costs. Furthermore, such design characteristics have the potential to increase accessibility to those in need.

Finally, the present dissertation adds to the growing literature on HPA function and affective disorders, with important clinical implications. With evidence that prevention efforts such as RUSH can result in changes to diurnal HPA axis regulation, further long-term follow-up

of such populations is required to determine whether such changes translate into reduced risk for later psychopathology. Additionally, results contribute to a growing body of evidence that biomarkers, such as HPA axis functioning influence how individuals respond to their environment. The concept applies not only to contexts of adversity, but also advantage in the form of preventive interventions. These findings have important implications for future research, as such information can be used to adapt intervention programs to better meets the needs of the individual. For example, information about individuals' susceptibility to intervention can be used to modify programming in terms of its duration (i.e., length), frequency (i.e., number of sessions), and intensity (i.e., target youth, parents, or both). Adapting interventions to the needs of the individual may increase program efficacy, improving mental health and psychosocial outcomes, while also considering the economic bottom line.

Conclusions

As emphasized throughout, BD is a serious and potentially debilitating mental illness that can result in a wide array of negative consequences. Preventive interventions that aim to ameliorate risk factors in youth at risk for developing BD demonstrate general efficacy. While programs have reported improved mental health and psychosocial outcomes in youth as well as their caregivers, prevention research in this area is limited by a lack of replication and few RCT studies with large sample sizes. Promising outcomes in the field underscore the need for continued research to solidify the empirical basis for prevention programs, followed by increased efforts to increase program accessibility and feasibility, generating greater outreach to those in need.

Overall, increasing evidence indicates that the HPA axis is a neuroendocrine system amenable to positive and promotive interventions. HPA axis function may also represent an

indicator of children who are most sensitive to changes in the family environment. Given that cortisol levels can be measured via minimally invasive procedures and stand to communicate valuable information with respect to individual sensitivity to environment, its use may prove extremely fruitful for future program development and implementation. Future research that steps away from a 'one size fits all' approach and aims to increase fit between the needs of the individual and programming, by considering such information, will be imperative to maximizing program effectiveness and efficiency.

Appendix A

Table 4. Effects of baseline diurnal cortisol and internalizing symptoms on internalizing behaviours over time in the OBD.

	a) CAR				b) Total Cortisol Output				c) Diurnal Cortisol Slope			
	Intercept (Baseline)		Slope (Time)		Intercept (Baseline)		Slope (Time)		Intercept (Baseline)		Slope (Time)	
	Coefficient (SE)	T-Ratio	Coefficient (SE)	T-Ratio	Coefficient (SE)	T-Ratio	Coefficient (SE)	T-Ratio	Coefficient (SE)	T-Ratio	Coefficient (SE)	T-Ratio
Level 1 (β_0; β_1)	24.57 (2.00)	12.26***	-0.27 (0.21)	-1.28	24.57 (2.00)	12.26***	-0.27 (0.21)	-1.28	24.57 (2.00)	12.26***	-0.27 (0.21)	-1.28
Level 2: Main effects												
Intercept	24.54 (0.56)	44.07***	-0.25 (0.19)	-1.34	24.54 (0.58)	42.52***	-0.25 (0.18)	-1.40	24.51 (0.58)	42.25***	-0.24 (0.19)	-1.29
Cortisol (P1)	1.00 (0.59)	1.70	0.33 (0.14)	2.32*	-0.42 (0.53)	-0.78	0.48 (0.26)	1.89ǂ	-0.11 (0.46)	-0.24	-0.42 (0.13)	-3.35**
Internalizing (P1)	10.24 (0.47)	22.01***	-0.21 (0.12)	-1.71	9.88 (0.44)	22.22***	-0.15 (0.13)	-1.10	10.04 (0.40)	25.25***	-0.19 (0.10)	-1.90ǂ
SES	-0.45 (0.50)	-0.90	-0.29 (0.13)	-2.31*	0.06 (0.58)	0.10	-0.42 (0.18)	-2.34*	-0.21 (0.52)	-0.41	-0.40 (0.11)	-3.51**

Notes. CAR – cortisol awakening response. AUC – area under the curve. P1 – phase 1. SES – socioeconomic status. SE - standard error.

ǂ $p = .07$; * $p < .05$; ** $p < .01$; ***$p < .001$.

Appendix B

Table 5. Effects of baseline diurnal cortisol levels on externalizing behaviours in the OBD.

	a) CAR				b) Total Cortisol Output				c) Diurnal Cortisol Slope			
	Intercept (Baseline)		Slope (Time)		Intercept (Baseline)		Slope (Time)		Intercept (Baseline)		Slope (Time)	
	Coefficient (SE)	T-Ratio	Coefficient (SE)	T-Ratio	Coefficient (SE)	T-Ratio	Coefficient (SE)	T-Ratio	Coefficient (SE)	T-Ratio	Coefficient (SE)	T-Ratio
Level 1 (β_0; β_1)	18.84 (2.22)	8.48***	-0.16 (0.25)	-0.63	18.84 (2.22)	8.48***	-0.16 (0.25)	-0.63	18.84 (2.22)	8.48***	-0.16 (0.25)	-0.63
Level 2: Main effects												
Intercept	18.86 (2.13)	8.87***	-0.17 (0.25)	-0.67	18.86 (2.09)	9.03***	-0.17 (0.25)	-0.67	18.86 (2.12)	8.88***	-0.17 (0.25)	-0.67
Cortisol (P1)	-0.35 (2.29)	-0.15	0.15 (0.25)	0.59	-2.30 (2.41)	-0.95	0.08 (0.28)	0.27	-0.71 (2.90)	-0.25	-0.09 (0.30)	-0.31
SES	3.43 (1.47)	2.33*	0.14 (0.18)	0.74	4.25 (1.59)	2.67*	0.15 (0.19)	0.77	3.00 (1.39)	2.16*	0.13 (0.19)	0.70

Notes. CAR – cortisol awakening response. AUC – area under the curve. SES – socioeconomic status. SE - standard error.
* $p < .05$; ** $p < .01$; ***$p < .001$.

Appendix C

Table 6. Effects of baseline diurnal cortisol levels on internalizing and externalizing behaviours in healthy controls.

	a) CAR				b) Total Cortisol Output				c) Diurnal Cortisol Slope			
	Intercept (Baseline)		Slope (Time)		Intercept (Baseline)		Slope (Time)		Intercept (Baseline)		Slope (Time)	
Internalizing	Coefficient (SE)	T-Ratio	Coefficient (SE)	T-Ratio	Coefficient (SE)	T-Ratio	Coefficient (SE)	T-Ratio	Coefficient (SE)	T-Ratio	Coefficient (SE)	T-Ratio
Level 1 (β_0; β_1)	21.10 (1.94)	10.89***	-0.36 (0.14)	-2.54*	21.10 (1.94)	10.89***	-0.36 (0.14)	-2.54*	21.10 (1.94)	10.89***	-0.36 (0.14)	-2.54*
Level 2: Main effects												
Intercept	21.12 (1.92)	10.99***	-0.36 (0.14)	-2.64*	21.09 (1.93)	10.94***	-0.36 (0.14)	-2.56*	21.13 (1.93)	10.93***	-0.36 (0.14)	-2.56
Cortisol (P1)	1.14 (1.32)	0.87	-0.18 (0.11)	-1.66	0.38 (2.05)	0.19	0.07 (0.13)	0.54	0.76 (2.11)	0.36	0.14 (0.12)	1.19
Externalizing												
Level 1 (β_0; β_1)	14.44 (1.36)	10.59***	-0.01 (0.15)	-0.10	14.44 (1.36)	10.59***	-0.01 (0.15)	-0.10	14.44 (1.36)	10.59***	-0.01 (0.15)	-0.10
Level 2: Main effects												
Intercept	14.43 (1.36)	10.63***	-0.02 (0.15)	-0.11	14.45 (1.36)	10.61***	-0.01 (0.15)	-0.09	14.49 (1.34)	10.84***	-0.02 (0.15)	-0.10
Cortisol (P1)	-0.33 (1.20)	-0.28	-0.07 (0.10)	-0.73	-0.54 (1.25)	-0.43	-0.07 (0.11)	-0.62	1.57 (0.94)	1.67	-0.01 (0.07)	-0.12

Notes. CAR – cortisol awakening response. AUC – area under the curve. P1 - phase 1. SES – socioeconomic status. SE - standard error.

* $p < .05$; ** $p < .01$; ***$p < .001$.

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