Interpersonal functioning in the offspring of parents with bipolar disorder: Developmental antecedents and relationship to cortisol levels

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ABSTRACT

Interpersonal functioning in the offspring of parents with bipolar disorder: Developmental antecedents and relationship to cortisol levels

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The offspring of parents with bipolar disorder (OBD) are at high risk for the development of affective disorders. Poor interpersonal functioning, as evidenced by persistent difficulties in establishing and maintaining satisfying relationships, may represent a key link between early family risk factors and the development of affective disorders. Interpersonal difficulties might also explain the high salivary cortisol levels observed in the OBD compared to the offspring of parents without mental disorders (controls). In this dissertation, the developmental antecedents of poor interpersonal functioning and its relationship to cortisol levels in the natural environment were examined among the OBD and controls. The first study examined whether parents' personality, specifically high neuroticism, predicted poor interpersonal functioning among the offspring 10 years later, and whether the relationship between parents' personality and offspring functioning was mediated by behavioral problems in middle childhood. High neuroticism and low agreeableness in the parents predicted poor interpersonal functioning in their offspring in late adolescence-early adulthood. The offspring's externalizing and internalizing problems in middle childhood partially mediated the association between parents' personality and offspring interpersonal functioning. The second study sought to determine if interpersonal functioning and episodic stress moderated the relationship between cortisol levels in the natural environment and risk status, defined as having a parent with bipolar disorder. The OBD who experienced high interpersonal chronic stress displayed a larger cortisol rise

following awakening than the OBD reporting low interpersonal chronic stress. The OBD who experienced severe interpersonal episodic stress exhibited higher levels of daytime cortisol than the OBD reporting interpersonal episodic stress of mild severity. Importantly, none of the above relationships were detected in the controls. The findings provide evidence of a biological sensitivity to interpersonal stress in the OBD, as evidenced by increased levels of awakening and daytime cortisol, which may underlie the susceptibility to affective disorders among the OBD. Overall, these studies highlight the importance of interpersonal dysfunction as a marker of vulnerability for the affective disorders. Importantly, the pattern of results emphasizes the need for targeted, early interventions aimed at increasing familial stability and stress management before the development of behavioural problems and chronic interpersonal difficulties.

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Caroline Ostiguy conducted some of the interviews (data collection), the statistical analyses, and wrote the first draft of the manuscript. Mark Ellenbogen, Sheilagh Hodgins, and Caroline Ostiguy edited subsequent versions of the manuscript. All authors contributed to and approved the final manuscript.

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1. INTRODUCTION

From infancy to adulthood, the negative consequences of having a parent with an affective disorder can be detected among their offspring (for reviews, see Beardslee, Versage, & Gladstone, 1998; Downey & Coyne 1990; Goodman & Gotlib, 1999). In the past thirty years, there has been a particular interest in the heightened risk for psychopathology and interpersonal difficulties in the offspring of parents having an affective disorder. The bulk of the research on this topic has focused on the children of depressed parents. The offspring of parents with bipolar disorder (OBD) have rarely been examined, despite the relatively high prevalence of bipolar disorders in the population (i.e., around 2.1%, Merikangas et al., 2007). We cannot assume that the literature for the offspring of parents with depression generalizes to the OBD, as it is likely that many of the risk factors associated with affective disorders are different in the offspring of depressed parents compared to the OBD (e.g., Hammen, 1991a). The small body of literature to date in the OBD confirms this suspicion, suggesting that the OBD face unique challenges.

The present thesis focuses on interpersonal functioning and stress in the OBD, who are at increased risk for developing affective disorders and other mental disorders (DelBello & Geller, 2001). By examining high-risk offspring, insight can be gained into the vulnerability factors associated with a disorder. The identification of risk factors and problematic developmental trajectories can help develop prevention and intervention programs, interrupting the intergenerational transmission cycle, and ultimately increasing functioning and the quality of life in these at-risk individuals (Beardslee & Gladstone, 2001; Beardslee et al., 1997; Belardinelli et al., 2008; Serbin & Karp, 2004).

1.1 Affective disorders: Prevalence and societal costs

The most common and most studied affective disorder is major depression. Recent large-scale population surveys, such as the National Comorbidity Survey Replication (NCS-R) have estimated that major depressive disorder has a point-prevalence of 6.6% and a lifetime prevalence of 16.9% in individuals 18 or older (Kessler, Chiu, Demler, Merikangas, & Walters, 2005). Age of onset most commonly occurs in the twenties and thirties, although the distribution in age of onset in remarkably wide, with a significant number of cases reported in later life (Kessler & Wang, 2008). In addition to the high prevalence, recurrence rates of depression are as high as 80%, and 60% of persons with depression report significant role impairment (Kessler et al., 2003). The World Health Organization's (WHO) Global Burden of Disease study ranks depression as the leading global cause of years lost due to disability (Murray & Lopez, 1997).

Bipolar disorders (BD) are characterized by extreme mood swings, or episodes, of mania, hypomania, and depression. Episodes of mania and hypomania are defined by periods of elevated mood or irritability. To meet diagnosis for a manic episode, one must also show an additional three symptoms (four symptoms if mood is irritable) among the following: grandiosity or increased self-esteem, reduced need for sleep, pressure to talk, flight of ideas, distractibility, increased involvement in pleasurable activities and increased involvement in goal-directed activities (American Psychiatric Association, 1994). Symptoms have to be present for at least one week in order to be considered as part of an episode, or they have to be severe enough to lead to a hospitalization if they are present for less than a week (APA, 1994). Only one episode of mania is necessary for a diagnosis of what is referred to as "BD

I". A BD II diagnosis is used to describe a milder form of BD, which requires at least one episode of hypomania (a manic episode associated with less impairment and lasting less than a week) and one episode of major depression.

Lifetime prevalence rates of BD have been reported as high as 2.1%, with an additional 2.4% exhibiting clinically significant symptoms of BD that do not meet full diagnostic criteria for the disorder (i.e., cyclothymia, BD not otherwise specified; Merikangas et al., 2007). The age of onset is typically late adolescence and early adulthood (Burke, Burke, Regier, & Rae, 1990; Weissman et al., 1996), with up to 60% of individuals with BD reporting onset before age 21 (e.g., Chengappa et al., 2003). Unlike depression, the prevalence of the disorder among males and females is roughly equivalent (Weissman et al., 1996). For persons diagnosed with BD, the mean number of lifetime episodes is well over 60 – the equivalent of over 10 years spent in an episode (Merikangas et al., 2007).

BD not only exerts a high cost on the individual, but on society as a whole (Kupfer, 2005). In 2001, BD was ranked as the ninth leading cause of years lived with disability (World Health Organization, 2001) and is expected to become the sixth cause of disability by 2020 (Murray & Lopez, 1997). Furthermore, in the National Comorbidity Survey Replication (NCS-R) study, almost all BD participants met criteria for another mental disorder (Merikangas & Kalaydjian, 2007). Perhaps even more remarkable is the staggering 85% of participants diagnosed with BD I or BD II who also met criteria for at least two other diagnoses (Merikangas & Kalaydjian, 2007). In a sample of 400 individuals hospitalized for BD, Cassidy, Ahearn and Carroll (2001) found that almost 60% of the sample had a current or past history of substance abuse. In addition, Fan and Hassell (2008) reviewed 32 studies examining personality disorders in individuals with BD and found a significantly higher rate

of axis II psychopathology in BD compared to the general population. It is therefore not surprising that BD is associated with a heavy use of health services, welfare, and disability benefits (Judd & Akiskal, 2003; McPherson, Dore, Loan, & Romans, 1992). Recent studies have also shown that patients with BD have, on average, 2.3 times the rate of mortality compared to the general population, with higher rates of suicide, cardiovascular diseases, and accidents (Angst, Stassen, Clayton, & Angst, 2002; Brodersen, Licht, Vestergaard, Olesen, & Mortensen, 2000). Other medical problems comorbid with BD include thyroid disease, diabetes mellitus, and obesity (Krishnan, 2005). Clearly, there is a pressing need to better understand the etiology of these disorders. In the sections that follow, important etiological factors will be briefly described.

1.2 Aetiology of the affective disorders

The affective disorders are heterogeneous in their presentation and their aetiology is complex and multifactorial. Research to date seems to reflect different developmental trajectories leading to the same outcome, a concept known as "equifinality" (Cicchetti & Toth, 1995). The literature on this topic is too vast to review in great detail, so only an overview is presented below.

1.2.1 Genetic factors

Family studies have revealed a clustering of individuals with affective disorders in some families (Kendler, Gatz, Gardner, & Pedersen, 2006b; McGuffin et al., 2003; Todd et al.,

1996). Examining the familial and intergenerational aspect of depression and BD is an important step in understanding what factors contribute to the intergenerational transmission of the disorders.

The familial nature of major depression has been examined extensively. A meta-analysis aggregating the data of five large studies revealed an odds ratio of 2.84 for the risk of depression in first-degree relatives of individuals with depression, compared to individuals without a family history of depression (Sullivan, Neale, & Kendler, 2000). Specifically for the transmission of the disorder across generations, Rice, Harold, and Thapar (2002) reported an odds ratio of 3.98 for the risk of depression in the offspring of parents with depression compared to offspring whose parents never had a psychiatric diagnosis. However, family studies cannot distinguish between genetic and shared environmental transmission; for instance, parents transmit both their genes and family environment to their children. Twin studies have been used to disentangle genetic and environmental influences on depression. Concordance rates are approximately 20% for dizygotic twins and 46% in monozygotic twins; heritability estimates range widely, from 11% to 72%, with the majority of studies providing an estimate around 40% (where 100% would suggest complete heritability; Kendler, Neale, Kessler, Heath, & Eaves, 1992; 1993; McGuffin et al., 1996, Rice et al., 2002). Overall, twin studies appear to indicate that a mixture of genetic and shared environmental factors contribute to the development of depression.

There are fewer twin studies of BD than of depression, and studies are limited by small samples sizes. From four well-designed and rigorous studies, concordance rates ranged from 5% to 19% for dizygotic twins and 39% to 67% in monozygotic twins; the heritability estimates ranged from 59% to 87% (Bertelsen, Harvald, & Hauge, 1977; Cardno et al., 1999;

Kendler, Pedersen, Johnson, Neale, & Mathe, 1993; McGuffin et al., 2003). Heritability estimates, therefore, are higher for bipolar disorder than for depression (for review, see Smoller & Finn, 2003). Another difference between the disorders is that family members of someone with BD are at risk of developing both BD and depression (McGuffin, Katz, & Aldrich, 1986), but family members of someone with major depression are no more likely to develop BD than the general population. Despite the evidence of genes' involvement in the intergenerational transmission and development of affective disorders, few specific genes have been consistently identified (for a review, see Kato, 2007).

Taken together, the intergenerational transmission of affective disorders could be due to the direct transmission of genes associated with the disorders. However, it is also possible that children inherit traits or vulnerability factors to affective disorders, such as cognitive, behavioural or interpersonal markers that, in turn, increase the risk for the development of affective disorders. In a way, these characteristics could lead children to select or respond to certain environments, increasing their levels of stress (Rutter, 2007). Temperament, low self-esteem, and neuroticism are only a few examples of characteristics through which the genetic vulnerability to affective disorders could be transmitted.

1.2.2 Biological factors

Although beyond the scope of the thesis, a number of biological abnormalities have been identified as putative risk factors for the affective disorders. Neurobiological abnormalities in the serotonergic system (Furlong et al., 1998; Lasky-Su, Faraone, Glatt, & Tsuang, 2005), dysfunctions in the circadian rhythm and sleep (Krystal, Thakur, & Roth, 2008; Malkoff-

Schwartz et al., 2000; Shen, Alloy, Abramson, & Sylvia, 2008), structural and functional changes in the prefrontal-limbic neural circuitry (McDonald et al., 2004; Monkul, Brambilla, Nery, Hatch, & Soares, 2007), and a number of neuro-hormonal anomalies (Birmaher et al., 2000; Gold, Goodwin, & Reus, 1978) have been identified. One area of particular interest is the hypothalamic-pituitary-adrenal (HPA) system (e.g., Ellenbogen, Hodgins, Linnen, & Ostiguy, 2011), but a more detailed description of the HPA axis and its association with the affective disorders is presented in Chapter 3. Many of the findings thus far should be interpreted cautiously, as the search for biological markers is complicated by the possible effects of illness severity and chronicity, medication use, and comorbid substance abuse. Moreover, longitudinal studies are needed to fully assess the significance of the identified biological abnormalities in BD.

1.2.3 Stress

1.2.3.1 Stressful negative life events

One of the most important factors examined in the aetiology of affective disorders is stress (for review, see Paykel, 2001). Stressful life events (SLEs) have been defined as "circumstances punctually situated in time that induce stress and require the individual to use adaptation mechanisms" (Ezquiaga, Ayuso Gutierrez, & Garcia Lopez, 1987; p. 136). To date, SLEs have been shown to play a role in the onset and relapse of depression (e.g., Kendler, Karkowski, Prescott, 1999). As described above, most of the work has focused on major depression, and there is less research on BD (for review, see Kelly, Hlastala & Frank, 2007; Paykel, 2003). Below, we review the literature on SLEs in individuals with BD.

From the limited number of studies that have examined the association between stress and BD, very few have focused on the initial onset of BD itself. Hillegers et al. (2004) measured SLEs retrospectively in a sample of adolescent OBD and found that overall stress levels were associated with a 10% increase in the risk of disorder onset. Horesh and Iancu (2010) found that both individuals with depression and BD experienced more stress during the year prior to their first episode compared to control participants. Both studies are limited by retrospective recall of stressors (Johnson & Roberts, 1995), but provide some support for the aetiological importance of stress in BD.

Given the difficulties associated with studying the onset of a disorder, most studies have focused on episode recurrence or relapse. Studies employing rigorous, interview-based assessments of SLEs have generally found an association between stress and episode onset (Bebbington et al., 1993; Ellicott, Hammen, Gitlin, Brown, Jamison, 1990; Hammen & Gitlin 1997; Hunt, Bruce-Jones, Silverstone, 1992; for exceptions see Chung, Langeluddecke, & Tennant, 1986; McPherson, Dore, Loan, & Romans, 1993). For instance, Ellicott and colleagues (1990) prospectively examined 61 patients with BD over two years. Controlling for compliance with medication, they found that participants who experienced low or average levels of SLEs were not at increased risk for relapse. However, individuals with high levels of stress had a 4.53 greater risk for relapse. Finally, SLEs have been shown to impede symptomatic and functional recovery (Kim, Miklowitz, Biuckians, & Mullen, 2007; Yan-Meier et al., 2011).

1.2.3.2 Stress generation theory

Constance Hammen (1991b) developed the stress generation theory, which proposes a bidirectional association between stress and depression. The theory is largely based on research examining SLEs in women who had either a diagnosis of unipolar depression, BD, a chronic physical illness, or no disorder (controls). In this seminal study (Hammen, 1991b), depressed women reported more dependent SLEs than the three other groups of women. Dependent life events were defined as "almost certainly or certainly due to the behaviors or characteristics of the person" (Hammen, 1991b, p. 557). Depressed women also reported more stressful interpersonal events than all the other groups. Hammen concluded that depressed individuals are more prone to create stressors that are in part dependent on their own behaviours and interpersonal in nature than individuals who are not depressed. This propensity to generate SLEs leads depressed individuals into a bidirectional cycle of depression and stress (Hammen, 2005). In other words, depressed individuals generate SLEs that can exacerbate their symptoms; when symptoms remit, the creation of SLEs can precipitate the recurrence of depressive symptomatology. In fact, women in remission have been found to have worse interpersonal functioning than women who have never been depressed, but similar functioning to currently depressed women (Hammen & Brennan, 2002), which suggests that SLEs are not just a consequence of current depressive symptoms.

Fewer studies have tested the stress generation theory in samples having BD. Hammen (1991b), found that women with BD experienced less dependent and interpersonal events than women with unipolar depression. Since then, two studies confirmed Hammen's initial finding that the theory does not extend to BD (Grandin, Alloy, & Abramson, 2007;

Reilly-Harrington, Alloy, Fresco, & Whitehouse, 1999). In contrast, a recent, prospective examination of the stress generation theory in individuals suffering from a bipolar spectrum disorder found support for the theory (Bender, Alloy, Sylvia, Urosevic, & Abramson, 2010). However, the authors suggest that the stress generation theory be extended to include positive events as well. Indeed, participants with BD in a depressive episode did not generate more negative, dependent SLEs, but experienced fewer positive interpersonal events than controls. Participants in a hypomanic episode experienced more dependent positive and negative interpersonal events than controls. Another study examined parents with BD and parents with no mental disorders and divided them among those with high and low neuroticism (Ellenbogen & Hodgins, 2004). Individuals with BD who were also high on neuroticism reported more dependent stressors than individuals with BD who were low on neuroticism. In a subsequent study of this sample (Ostiguy et al., 2009), the OBD did not experience more dependent life events, but did experience more severe independent life events compared to controls. These findings differ from studies of the offspring of parents with depression (Adrian & Hammen, 1993; Hammen, 1991a), who tend to generate more SLEs that are dependent on their own behaviour.

Taken together, these findings suggest that the OBD do not generate stress in their lives but rather are exposed to stress that may in part be due to the unstable environment of living with an affectively-ill parent. Clearly, there is a need for more studies exploring stress exposure and stress generation in individuals with BD and their offspring, as this knowledge could greatly impact prevention and treatment targets (e.g., Bockting et al., 2006).

1.2.3.3 Chronic stress

Chronic stress is defined as "adverse circumstances that act uninterruptedly over a prolonged time" (Ezquiaga et al., 1987; p. 136), as opposed to SLEs, which are acute and time-limited. In their seminal study, Brown and Harris (1978) described that chronic stress ("major difficulties") was associated with the onset of depression in women. Similarly, in a retrospective study, individuals diagnosed with depression were seven times more likely to have experienced a chronic problem prior to the onset of depression compared to non-affected individuals (Rojo-Moreno, Livianos-Aldana, Cervera-Martinez, Dominguez-Carabantes, & Reig-Cebrian, 2002). Beyond depression onset, chronic stress has also been associated with depressive symptoms; for example, McGonagle and Kessler (1990) have found chronic stress to be a better predictor of depressive symptoms than SLEs.

It is possible that chronic and episodic stress interact in predicting relapse. Hammen and colleagues (2009) tested this hypothesis in a large sample of depressed and non-depressed women. First, they found that chronic stress predicted depressive episode onset, although with less power than episodic stress. Second, they found that chronic stress moderated the effects of SLEs, such that high levels of chronic stress amplified the association between episodic stress and depression. Similar results were found in a small sample of older adults; high neuroticism and chronic stress both increased the risk of sub-clinical or clinical depression onset in individuals experiencing SLEs (Ormel, Oldehinkel, & Brilman, 2001). Finally, in a recent study of young women at high-risk for depression, the combination of interpersonal chronic and episodic stress – but neither type of stress alone –

was associated with elevated cortisol levels in the natural environment (Marin, Martin, Blackwell, Stetler, & Miller, 2007), a marker of risk for depression (Ellenbogen et al., 2011).

To our knowledge, only one study specifically examined chronic stress in individuals with BD (Kim et al., 2007). In a sample of adolescent OBD diagnosed with BD, chronic stress in family and romantic relationships predicted less improvement in depressive and manic symptoms following an intervention combining psychoeducation and medication (Kim et al., 2007). My colleagues and I (Ostiguy & Ellenbogen, 2011) have recently undertaken a re-assessment of bipolar (n = 27) and control parents (n = 42), as part of the longitudinal project. Preliminary analyses of the UCLA Life Stress Interview (Adrian & Hammen, 1993; Hammen, 1991a) suggest that parents with BD experienced more interpersonal ($F = 7.15$, $p < 0.01$) and non-interpersonal chronic stress ($F = 22.91$, $p < 0.001$) in the six months prior to the clinical interview compared to control parents. Unfortunately, these data do not inform us as to the predictive power of chronic stress on relapse or time to recovery. In light of these findings, a comprehensive investigation of stress in individuals suffering from an affective disorder should therefore include a simultaneous examination of both SLEs and chronic stress.

1.2.4. The interpersonal context of affective disorders

1.2.4.1 Interpersonal theories of depression

Over the last thirty years, interpersonal factors have become more central to our understanding of psychopathology. The study of the interpersonal context in psychopathology started in the 1970s, when interpersonal theories of depression brought a

new perspective to the study of affective disorders by examining how the quality of individuals' interpersonal relationships, the availability of their support networks, and their styles of social interaction are associated with well-being. Such theories either posit that (1) positive interpersonal relationships buffer individuals against the deleterious impact of stressors on well-being (e.g., Brown & Harris, 1978), and/or (2) maladaptive interpersonal styles render certain individuals vulnerable to developing depressive symptoms (e.g., Van Orden, Wingate, Gordon, & Joiner, 2005).

Theories such as the social origins of depression (Brown & Harris 1978), the interactional model of depression (Coyne, 1976), the contagion effect (Joiner, Alfano, & Metalsky, 1992; Joiner & Katz, 1999), Lewinsohn's behavioural theory of depression (Lewinsohn, 1974), Lewinsohn's revised integrative model of depression (Lewinsohn, Hoberman, Teri, & Hautzinger, 1985), and research on assortative mating (Merikangas, Prusoff, & Weissman, 1988) have all incorporated the interpersonal context into their explanation of depression. Overall, these models describe how depressed individuals' behaviours and symptoms can induce negative reactions and moods in their friends and family members, which can then exacerbate symptoms and create relationship problems. These theories have elicited new research exploring the relationship between interpersonal functioning and the affective disorders.

1.2.4.2 Interpersonal functioning in major depression and bipolar disorder

Interpersonal functioning can be defined as the ability to create and maintain satisfying interpersonal relationships with friends, family members, romantic partners, and colleagues.

Negative interpersonal relationships as well as deprivation of social contacts and support are associated with a host of psychological and physical negative outcomes (Baumeister & Leary, 1995; House, Landis, & Umberson, 1988), while positive relationships have been associated with good mental and physical health (e.g., Cacioppo et al., 2008). Intuitively, it makes sense that symptoms of depression and mania may lead to social difficulties. Social withdrawal, apathy, and reassurance seeking in depression or extravagant spending and sexual behaviours, reckless activities, and grandiose self-esteem in mania are only a few examples of symptoms that could create tensions with family members and friends (Goodwin & Jamison, 2007). However, social problems in individuals suffering from affective disorders persist even when the symptoms have subsided (e.g., Hammen & Brennan, 2002), suggesting that the affective disorders may be associated with chronic interpersonal problems.

Most of the research on interpersonal functioning has been carried out in depressed samples. Consistent with the interpersonal theories of depression, studies have found that depressed persons have poor interpersonal relationships (Joiner & Coyne, 1999; Sheeber, Hops, & Davis, 2001; Zlotnick, Kohn, Keitner, & Della Grotta, 2000). Marital stability and romantic relationships (for review, see Rao, Hammen, & Daley, 1999) and parenting (Goodman & Gotlib, 1999) are contexts in which depressed individuals show difficulties. For instance, women diagnosed with major depression or dysthymia displayed poor interpersonal functioning with spouses, children and extended family members (Hammen & Brennan, 2002). In the latter study, the interpersonal problems seemed stable, remaining even after the symptoms of depression had remitted, a finding that has been replicated a number of times, in men and women (Billings & Moos, 1986; Hammen, 1991a; Hammen & Brennan, 2002;

Keitner & Miller, 1990; Weissman & Paykel, 1974). Even people who experience mild symptoms of depression, but who do not meet diagnostic criteria, report interpersonal problems similar to what is seen in depressed individuals (Carnelley, Pietromonaco, & Jaffe, 1994; Gotlib, Lewinsohn, & Seeley, 1995). In a review of the literature on interpersonal functioning in women, Hammen (2003a) concludes that learned maladaptive interpersonal skills and the generation of interpersonal stressful life events, coupled with the importance of relationships in women (Cyranowski, Frank, Young, & Shear, 2000), lead to an interpersonal vulnerability to depression. In depressed women, this vulnerability could maintain depressive symptoms; in remitted women, it could play a role in the recurrence of depression.

Although much less research has been conducted in people with BD, the data nonetheless suggest that patients with BD also experience interpersonal difficulties during and between episodes. From the 1920s until the 1950s, bipolar patients were described as narcissistic, self-absorbed, noxious, irritable, exaggerated, and unaware, just to name a few (Blalock, 1936; English, 1949; Gibson, Cohen, & Cohen, 1959; Kraepelin, 1921). Beyond clinical observations, contemporary research has confirmed that individuals suffering from BD have impoverished social relationships compared to control individuals (Romans & McPherson, 1992). For example, Coryell and colleagues (1993) found that compared to controls, individuals with BD were half as likely to marry, and those who were married, were twice as likely to divorce (see also Suppes et al., 2001).

Sadly, the impairment in functioning, in both social and other domains, is enduring among patients with an affective disorder (Bauwens, Tracy, Pardoen, Vander Elst, & Mendlewicz, 1991; Coryell et al., 1993; Judd et al., 2008; MacQueen, Young, & Joffe, 2001). MacQueen et al. (2001) compiled studies from the last 25 years and concluded that 30

to 60% of BD patients experience significant interpersonal problems between episodes. It is therefore well-established that BD individuals experience interpersonal difficulties not only during episodes as a result of their symptoms, but also between episodes. Perhaps even more startling is the predictive power of poor interpersonal problems. In remitted patients with depression or BD, levels of social dysfunction were associated with recurrence of an affective episode, above and beyond clinical characteristics such as past number of episodes, age of onset, etc. (Bauwens, Pardoen, Staner, Dramaix, & Mendlewicz, 1998; Staner et al., 1997). Similarly, perceived lack of social support has been shown to predict relapse of a depressive episode in individuals with BD over a one-year period (Cohen, Hammen, Henry, & Daley, 2004). Interestingly, the association between social difficulties and episode recurrence seems to be stronger for depressive episodes than manic or hypomanic episodes (Cohen et al., 2004; Coryell et al., 1998). These findings highlight the importance of understanding interpersonal functioning as an important component of treatment and preventative interventions. Longitudinal studies are necessary to better understand its developmental antecedents and to determine whether interpersonal problems represent a risk factor or consequence of having a mental disorder.

1.2.4.3 Interpersonal functioning as a risk factor for the affective disorders

A few longitudinal studies have examined whether interpersonal dysfunction plays a role in the onset of affective disorders, but no consensus has been reached. Some studies have found an association between social problems and the onset of depressive symptoms (Eberhart, Shih, Hammen, & Brennan, 2006; Hammen & Brennan, 2001; Segrin, 2000), while others

have not (e.g., Lewinsohn et al., 1994). For instance, in a sample of adolescent girls, conflicts with family members were a predictor of depressive symptoms and episodes over the following two years (Eberhart & Hammen, 2006). Other interpersonal factors such as poor peer relationships and an inability to form close relations with others were associated with depressive symptoms over a six-month follow-up. Similarly, romantic relationship stressors predicted depressive symptoms in college women over a four-week period (Eberhart & Hammen, 2010).

In high-risk samples, interpersonal problems may represent a vulnerability factor or an early marker of affective disorders (Cicchetti & Schneider-Rosen, 1986; Goodman, Brogan, Lynch, & Fielding, 1993). Hammen and colleagues (2003) examined the association between depressive symptoms and interpersonal functioning in a sample of 15-years old at high and low risk for depression based on family history. Although social problems were associated with depressive symptoms in both groups, the association was stronger for the high-risk group. Furthermore, youth's interpersonal problems were associated with depression concurrently (Hammen, Brennan, & Shih, 2004; Hammen, Shih, & Brennan, 2004) and longitudinally (Hammen, Brennan, Keenan-Miller, Hazel, & Najman, 2010). Recently, women having at least one copy of the short allele in the promoter region of the serotonin transporter gene (associated with vulnerability to stress; Caspi et al., 2003) were more likely to report depressive symptoms when experiencing chronic interpersonal problems at home than women having two copies of the long allele (Hammen et al., 2010). These data suggest that women with a genetic vulnerability are more prone to depression when they have interpersonal difficulties.

1.2.5 Summary

There is unequivocal evidence that SLEs and chronic stress play a role in the course of affective disorders. However, there is a need for longitudinal studies of high-risk cohorts to understand the timing and directionality of the association between different types of stress and affective disorders. Additionally, studies investigating putative mechanisms through which stress impacts risk are required to better inform prevention and treatment research.

1.3 Studying premorbid risk factors: The offspring of parents with bipolar disorder

The study of high-risk offspring has been employed for almost 30 years in the field of psychopathology. They offer a unique opportunity to better understand the risk factors and early signs and course of a disorder. Moreover, high-risk studies are critical for the development of targeted, early interventions aimed at reducing the prevalence of affective disorders (Goodwin & Jamison, 2007).

1.3.1 Offspring of parents with depression

Across multiple studies, rates of depression in the offspring of depressed parents range from 20% to 40% (Hammen et al., 2003; Keller et al., 1986; Warner, Weissman, Fendrich, Wickramaratne, & Moreau, 1992). Offspring are also at higher risk for substance abuse/dependence disorders and anxiety disorders (Lieb, Isensee, Hofler, Pfister, & Wittchen, 2002; Weissman, Wickramaratne, et al., 2006). Parental depression has been

associated with a host of negative cognitive, interpersonal, and neuroendocrine outcomes, from infancy to adulthood (for review, see Goodman & Tully, 2006). Overall, the offspring of depressed parents have a higher likelihood of suffering from a range of problems that may act as vulnerability factors to or as early markers of psychopathology (Goodman, 2007). A detailed review of this literature is beyond the scope of the thesis.

1.3.2 Offspring of parents with bipolar disorder

The subjective experiences of children who are raised by a mother or father with BD are unique:

> As I got older mom would disappear randomly... she would simply walk away from our house not to be seen for weeks. Sometimes she called a taxi. Sometimes she drove. That was scary because we knew she drank when she was manic and bad things happen when you mix alcohol and driving... a manic one at that.
>
> My dad went crazy when she was gone. He was so worried. He didn't know how to comfort my brother and I because he didn't know how to comfort himself. Every night without fail dad would wake my brother and I up and take us out to his truck. We spent nights driving around town looking for signs of my mom. He would drive everywhere, stopping at bars, everywhere. He would stop and buy my brother and I hot chocolate and cookies from the gas station. This became a normal thing in our family.
>
> Mom always came home. Sometimes a few days later… sometimes weeks. Sometimes she would call and ask to be picked up. Sometimes strange people would drop her off at our house. I knew it was bad but sometimes I wished she wouldn't come home. I was tired of the game, even as a kid. When she came home she was usually drunk. She would go to her room and my parents would yell for a long time. Then things would be quiet. For days. My brother and I tiptoed around the house and tried not to bug her. I was scared to see her. Once I put a note under her door telling her I was sorry for whatever I thought I had did *(sic)* to cause this.[1]

[1] See YogaMujer82, 2008.

In contrast to the large number of articles published on the offspring of depressed parents, there are fewer studies of the OBD. The OBD are 15 times more likely to suffer from a bipolar-spectrum disorder and five times more likely to develop a depressive disorder than offspring of parents with no mental disorders (Birmaher et al., 2009). DelBello and Geller (2001) reviewed the psychopathology literature in the OBD and reported that 5-67% of the OBD and 0-38% of control offspring will develop an affective disorder. OBD are also more likely to suffer from anxiety disorders, substance abuse, attention-deficit/hyperactivity disorder, and oppositional defiant disorder (Birmaher et al., 2009; DelBello & Geller, 2001; Hammen, Burge, Burney, & Adrian, 1990; Henin et al., 2005; Hillegers et al., 2005; Maziade et al., 2008; Reichart et al., 2004; Singh et al., 2007; Waters, Marchenko, & Smiley, 1983). Overall it is estimated that between 23% and 74% of all OBD will develop at least one mental disorder in their lifetime (Radke-Yarrow, Nottelmann, Martinez, & Fox, 1992). In the sections below, risk factors identified in the OBD will be reviewed. However, we first expand on the early home environment of children and adolescents growing up in a family with BD.

1.3.2.1 Family environment and parenting

Studies have found that parents with BD create a familial environment that is unstable, chaotic, and lacking in structure (Chang, Blasey, Ketter, & Steiner, 2001; Du Rocher Schudlich, Youngstrom, Calabrese, & Findling, 2008; Ellenbogen & Hodgins, 2004, 2009; Romero, Delbello, Soutullo, Stanford, & Strakowski, 2005). In addition, parents with BD have been found to have high scores on neuroticism, which is associated with fewer social

contacts, poor marital functioning, more verbal aggression, and the use of less problem-focused and more emotion-focused coping skills (Ellenbogen & Hodgins, 2004). Moreover, mothers with BD tend to have more negative interactions with their children than mothers without BD (Inoff-Germain, Nottelmann, & Radke-Yarrow, 1992; Meyer et al., 2006). A review of studies examining the OBD showed that stressful environmental factors such as parents' marital discord, poor quality of parenting, and the presence of a second parent with psychopathology were all associated with the development of disorders in the offspring (DelBello & Geller, 2001). One study showed that there is a direct association between parental BD and child BD; this association is mediated through family functioning (i.e., problem solving, communication, roles, affective involvement, and responsiveness; Du Rocher Schudlich et al., 2008). These findings suggest that OBD, in addition to being genetically at risk for the development of affective disorders, are exposed to an environment that is likely to create stress, discord, and instability, and thus, increase the risk of psychopathology and associated impairments. More research is needed however before stating confidently that dysfunctional family interactions contribute to the onset of affective disorders in the OBD (Jones & Bentall, 2008). Markers of vulnerability, described in the sections below, arise from this genetic and psychosocial context, and include behavioural, academic, neuropsychological, cognitive and social difficulties.

1.3.2.2 Behavioural and academic problems

The OBD experience a number of difficulties throughout stages of development. For instance, Hirshfeld-Becker et al. (2006) observed that the OBD, aged 2 to 6 years, exhibited

more disinhibition than the offspring of parents with depression or panic disorder. From middle childhood to adolescence, studies have demonstrated that the OBD have more internalizing and externalizing problems than controls (Ellenbogen, Hodgins, Walker, Couture, & Adam, 2006; Giles, DelBello, Stanford, & Strakowski, 2007), but some studies have found this only in the OBD diagnosed with affective disorders (Dienes, Chang, Blasey, Adleman, & Steiner, 2002). The OBD are also experiencing more attentional and behavioural problems (Carlson & Weintraub, 1993; Meyer et al., 2004) and suicidality (Klimes-Dougan et al., 1999) compared to children of parents with no disorders. During the school years, the OBD are also more likely to be put in special classes, have poor academic performance, and display deviant school behaviours (Henin et al., 2005; McDonough-Ryan et al., 2002).

1.3.2.3 Neuropsychological and cognitive abnormalities

Meyer and colleagues (2004) reported that the OBD who went on to develop BD in young adulthood were more likely to have shown impairment on the Wisconsin Card Sorting Test during adolescence. This deficit in executive functioning was replicated in two other samples of adolescent OBD who underwent extensive neuropsychological testing (Klimes-Dougan, Ronsaville, Wiggs, & Martinez, 2006; Maziade et al., 2009). In addition, studies showed that the OBD had higher verbal than performance IQ compared to control offspring (Decina et al., 1983; McDonough-Ryan et al., 2002), but this has not been replicated in all studies (Maziade et al., 2009; Winters, Stone, Weintraub, & Neale, 1981). Maziade and colleagues (2009) also found that the OBD showed a lower global IQ score compared to controls. Finally, the OBD exhibit attentional biases to emotional information, especially towards socially threatening

words, by taking longer to color-name these words on the Stroop task (Gotlib, Traill, Montoya, Joormann, & Chang, 2005). The OBD in the latter study also remembered more negative words on a recall test than control participants. Unfortunately, this study is based on small sample size and has not been replicated. In sum, a deficit in executive functioning (and related cognitive impairments) may represent an important marker of vulnerability, perhaps even an endophenotype (a genetically mediated marker of risk that represents the link between the gene and the complex disorder), in high-risk offspring. Speculatively, problems in executive function may underlie other regulatory functions, including the regulation of mood, HPA activity, and interpersonal functioning (e.g., Ellenbogen, 2005).

1.3.2.4 Maladaptive cognitive style and temperament

The OBD also seem to engage in maladaptive coping styles and exhibit distinctive temperament profiles. One of the earliest studies to examine cognition in the OBD found that the high-risk offspring were more likely to endorse a less positive self-concept and a more negative attributional style compared to the offspring of medically ill or control mothers (Jaenicke et al., 1987). It is unclear if the results are due to the risk status or to the presence of affective disorders in the OBD however, as the authors did not control for diagnoses. Similarly, adolescent OBD were found to have maladaptive coping skills (i.e., rumination), low self-esteem, and increased risk taking behaviours compared to control participants; this distinction, however, was only present between the OBD diagnosed with a current or past affective disorder and the controls (Jones, Tai, Evershed, Knowles, & Bentall, 2006).

Sensation seeking and a tendency to approach novel situations have also been found to be higher in the OBD (Chang, Blasey, Ketter, & Steiner, 2003; Nurnberger et al., 1988).

1.3.2.5 Interpersonal functioning

Some studies have found no impairment in functioning among the OBD (Anderson & Hammen, 1993; Hecht, Genzwurker, Helle, & van Calker, 2005; Klein, Depue, & Krauss, 1986; Linnen, aan het Rot, Ellenbogen, & Young, 2009; Reichart et al., 2007), while others have found evidence of maladjustment, such as decreased psychosocial functioning and poorer peer networks (Bella et al., 2011; Henin et al., 2005; Hodgins, Faucher, Zarac, & Ellenbogen, 2002; Ostiguy et al., 2009; Pellegrini et al., 1986; Zahn-Waxler, Cummings, McKnew, & Radke-Yarrow, 1984). We found that, compared to offspring of parents with no mental disorders, the OBD had more interpersonal problems even after controlling for affective disorders (Ostiguy et al., 2009). Interestingly, only the family relationship domain was significantly different between the OBD and control offspring: no group differences were reported on clinician ratings of close friendship and romantic relationships. A study by Reichart and colleagues (2007) is of particular interest, as it is a prospective, longitudinal study of 140 OBD. They found that social functioning was impaired only in the OBD who were aged 18 or over or were diagnosed with an affective disorder (unipolar depression or BD). The younger or non-affected offspring were not different than the offspring from the general population. Klein and colleagues (1986) found similar results; social adjustment was poor in the OBD diagnosed with cyclothymia, but not in the undiagnosed OBD or healthy controls. In sum, research to date highlights the presence of interpersonal problems in the

OBD, but the findings are inconsistent; longitudinal data are needed to clarify the link between poor interpersonal functioning and the development of affective disorders in these high-risk samples.

1.3.2.6 Summary and conclusions from the literature on the OBD

Research to date suggest that the OBD exhibit some behavioural and attention problems, neuropsychological abnormalities, maladaptive coping strategies, and interpersonal difficulties. Furthermore, the OBD grow up in an environment that is likely to be unstable and full of conflict, which, in combination with a genetic vulnerability, could increase the risk for affective disorders. Although studies have revealed a number of indicators of vulnerability, the research to date has been limited by methodological problems including small sample sizes and few developmental prospective studies. There is a clear need for further research to better understand the development and course of such difficulties, on their own and in relation to the development of psychiatric disorders. Examining problematic areas of functioning is critical in understanding the mechanisms and processes by which psychopathology develops and is maintained (Sroufe & Rutter, 1984).

1.4 Rationale and goals of the current studies

The sample examined in this dissertation is part of a longitudinal cohort of 105 families (208 parents and 146 offspring) originally recruited when the offspring were between 4 and 14 years of age, between 1996 and 1998. The cohort consists of families having a parent with a

diagnosis of bipolar disorder and families having parents with no mental disorder. Between 2006 and 2010, a two-wave re-assessment of the offspring sample was undertaken. The offspring, now aged between 14 and 28 years, were invited to the laboratory where they were interviewed by a clinical psychologist or experienced graduate student, underwent three days of saliva sampling to assess cortisol levels, and completed an information processing protocol (not described here). An identical protocol was repeated a year later for each offspring, but this is not included in the present thesis.

The goal of this dissertation was to examine longitudinal predictors and biological correlates of interpersonal functioning in the OBD. Interpersonal functioning is an important concept in developmental psychopathology, and it has been found to predict the development of affective disorders (e.g, Eberhart & Hammen, 2006). In the first study, I examined the impact of parents' neuroticism on behavioural problems during childhood and interpersonal functioning in late adolescence/early adulthood. Neuroticism has consistently been associated with interpersonal and occupational problems, stressful life events, ineffective coping strategies, and non-optimal parenting practices (Belsky & Barends, 2002); it is therefore a likely parental antecedent to negative outcomes in the offspring. The study tested a hypothesis where parental neuroticism leads to early behavioural problems in offspring that evolve over time into chronic interpersonal difficulties. A key goal of the study was to facilitate the development of a model explaining the transmission of vulnerability to affective disorders from one generation to the next. Such research could ultimately help us devise tools to identify the OBD at higher risk for psychopathology, as well as targeted early prevention interventions.

The goal of study 2 was to examine one putative consequence of poor interpersonal functioning: changes in the HPA axis, a biological system that is sensitive to social factors. Study 2 was designed to examine a possible mechanism that could explain why the OBD consistently secrete higher levels of salivary cortisol (Ellenbogen, Santo, Linnen, Walker, & Hodgins, 2010). Indeed, HPA axis-related abnormalities have been shown in depression and BD, as well as high-risk offspring (e.g., Deshauer et al., 2003; Ellenbogen et al., 2006; Plotsky, Owens, & Nemeroff, 1998; Mannie, Harmer, & Cowen, 2007). High levels of cortisol may be particularly meaningful in the aetiology of affective disorders as they prospectively predict the development of an affective disorder (Ellenbogen et al., 2011). Therefore, the goal of this study was to examine if interpersonal functioning and SLEs moderated the relationship between cortisol levels and risk status, defined as having a parent with BD. This research may provide clues as to the mechanisms implicated in the association between poor interpersonal functioning and the development of affective disorders, while contributing to the identification of targets for prevention intervention in the OBD.

2. PERSONALITY OF PARENTS WITH BIPOLAR DISORDER AND INTERPERSONAL FUNCTIONING AMONG THEIR OFFSPRING: A PROSPECTIVE 10-YEAR STUDY

2.1 Introduction

Early in development, the negative consequences of having a parent with an affective disorder can be detected among their offspring. For example, children of mothers with depression exhibit more negative affect, less positive affect, fewer vocalizations, less motor activity, less secure attachment, lower social competence, more internalizing and externalizing behaviours, and brain asymmetry compared to children of healthy mothers (Field, 2002; Jones, Field, Fox, Lundy, & Davalos, 1997; Murray, Fiori-Cowley, Hooper, & Cooper, 1996; Radke-Yarrow et al., 1992). Through middle childhood and adolescence, the offspring of mothers with depression continue to exhibit elevated rates of internalizing and externalizing problems (Elgar, Mills, McGrath, Waschbusch, & Brownridge, 2007), abnormalities in emotional information processing (Joormann, Talbot, & Gotlib, 2007), and elevated hypothalamic-pituitary-adrenal (HPA) functioning in the natural environment (Halligan, Herbert, Goodyer, & Murray, 2004). Less is known about the offspring of parents with bipolar disorder (OBD) in childhood (LaRoche, 1985), with one study suggesting lower rates of problem behaviours among OBD than among the offspring of parents with depression (Anderson & Hammen, 1993). Studies have shown that OBD, as compared to offspring of healthy parents, experience higher levels of episodic and chronic stress (Ostiguy et al., 2009), perform poorly on tests of executive function (Klimes-Dougan et al., 2006), exhibit attentional biases to emotional information (Gotlib et al., 2005), and show alterations in the functioning of the stress-sensitive HPA axis (Ellenbogen et al., 2006; Ellenbogen et al.,

2010). While these features distinguished OBD from offspring of parents with no mental disorder (i.e., offspring without a family history of BD; OFH-) in cross-sectional studies, little is known about factors and mechanisms operating in the early life of the OBD that contribute to their vulnerability for affective disorders later in life.

Neuroticism is a personality trait characterized by a propensity to experience negative emotions such as anger, sadness, guilt, and irritability (Costa & McCrae, 1992a). Individuals high in neuroticism struggle with interpersonal and occupational problems, generate stressful life events, and use ineffective coping strategies (Belsky & Barends, 2002; DeLongis & Holtzman, 2005; Ellenbogen & Hodgins, 2004; Watson, Gamez, & Simms, 2005). The trait of neuroticism, like other personality traits, affects parenting practices, and may thereby impact offspring functioning, as initially proposed by Belsky (1984) and subsequently supported by empirical findings (Prinzie, Stams, Dekovic, Reijntjes, & Belsky, 2009). For example, parents high in neuroticism displayed lower levels of smiling, talking, and touching with their infant than parents low on neuroticism (Zaslow, 1985). Similarly, mothers high in neuroticism exhibited a parenting style that was less warm, less responsive, and more intrusive than mothers low in neuroticism (Belsky, Crnic, & Woodworth, 1995; Clark, Kochanska, & Ready, 2000; Kochanska, Clark, & Goldman, 1997). High maternal neuroticism, assessed by self-report or observation, has been associated with defiance, anger, behavioural problems, and insecure attachment among offspring in early childhood (Kochanska et al., 1997). Moreover, adolescent and adult offspring of parents high, as compared to those low in neuroticism, were found to have an increased sensitivity to stressful life events, poorer mental health, more antisocial behaviours, and personal adjustment problems (Conger, Conger, Elder, & Lorenz, 1992; Elder, Caspi, & Downey, 1986; van Os &

Jones, 1999). Thus, evidence shows that high levels of neuroticism among parents are associated with non-optimal parenting practices and a broad range of negative outcomes among their offspring from early childhood through to early adulthood.

We have previously postulated a model to explain the associations between parents' personality and vulnerability to psychopathology among offspring of parents with bipolar disorder (BD; Ellenbogen & Hodgins, 2004), who are at high risk for the development of both major depression and BD (Birmaher et al., 2009; Hodgins et al., 2002; Lapalme, Hodgins, & LaRoche, 1997). We hypothesized that one facet of the genetic vulnerability for affective disorders is expressed as the trait of neuroticism (Kendler, Gatz, Gardner, & Pedersen, 2006a). That is, the child who inherits the genes associated with affective disorders inherits a tendency to react emotionally to stressors and daily hassles. This tendency is promoted by being raised by one or two parents with high levels of neuroticism who themselves display a pattern of over-reactivity to daily life events and ineffective coping with stress. The parents' behaviour creates a family environment that is stressful, chaotic, and unpredictable and that fails to teach the child appropriate skills for coping with stress (Chang et al., 2001; Ellenbogen & Hodgins, 2004). In addition, these parents do not provide adequate support and structure for their children (Ellenbogen & Hodgins, 2009). The family environment and parenting practices, we postulate, in interaction with a genetic vulnerability, lead to deficits in emotional, behavioural, and physiological regulation among the children (Derryberry & Rothbart, 1997; Ellenbogen & Hodgins, 2009). Thus parents with BD may transmit genes to their offspring that make them vulnerable to major affective disorders and as well, by their behaviour and parenting practices, create a family environment that enhances this genetic vulnerability. Similarly, the offspring who inherit a genetic

vulnerability for affective disorders, as they grow up, may seek out environments that are consistent with their own inability to cope with daily life and stress (Rutter, 2007; Rutter, Moffitt, & Caspi, 2006). In sum, the personality of parents is postulated to elicit a number of adverse environmental processes that have a negative impact on offspring directly and through gene-environment interplay.

We have previously examined the relationship between parents' neuroticism and functioning of OBD as compared to OFH-. This cross-sectional investigation showed that among the parents, a high level of neuroticism was associated with a broad range of difficulties, including poor social and occupational functioning, lower educational attainment, problems in intimate relationships, low levels of social support, more negative life events that they caused themselves, ineffective strategies for coping with stress, and non-optimal parenting practices (Ellenbogen & Hodgins, 2004). After controlling for parents' affective disorders, psychosocial functioning, and parenting practices, high levels of neuroticism in the parents was a robust predictor of internalizing and externalizing problems among the offspring in childhood. The present study was designed to follow-up on these findings, by examining the effects of parents' neuroticism on offspring's interpersonal functioning ten years later. The study also aimed to determine if the internalizing and externalizing problems exhibited in middle childhood mediated the association between parents' neuroticism and offspring's interpersonal functioning in late adolescence-early adulthood. It is posited that both internalizing and externalizing problems in childhood are important markers of risk for future affective disorders. In addition to the link between childhood externalizing problems and later BD (Carlson, Bromet, & Sievers, 2000), there is recent prospective evidence that among OBD childhood anxiety disorders double the risk of

developing an affective disorder in late adolescence or early adulthood (Duffy, Alda, Hajek, Sherry, & Grof, 2010). Thus, internalizing and externalizing problems in childhood are expected to be part of the developmental trajectory leading to interpersonal problems in late adolescence-early adulthood and subsequently to affective disorders.

Poor interpersonal functioning, which reflects persistent difficulties in establishing and maintaining satisfying relationships with family members, peers, colleagues, and romantic partners, may represent a key link between early family risk factors and the development of an affective disorder (Hammen, 2005). For instance, in a sample of 800 mothers and their 15-year-old offspring, adolescents' interpersonal difficulties were strongly related to their own level of depression and the association was more pronounced among the offspring of mothers with, than without, a diagnosis of depression (Hammen et al., 2003). Similarly, adult offspring of depressed parents were found to have poorer functioning at work, in their marriage, and with family members than the OFH- (Weissman, Warner, Wickramaratne, Moreau, & Olfson, 1997). Consequently, interpersonal functioning may play an important role in the transmission of depression from one generation to the next (Cicchetti & Toth, 1998; Goodman & Gotlib, 1999), through both genetic and environmental mechanisms.

The present study tested three hypotheses. First, based on our previous findings (Ellenbogen & Hodgins, 2004), we hypothesized that high neuroticism in parents, assessed when offspring were children, would predict interpersonal dysfunction in the offspring in late adolescence-early adulthood. Interpersonal functioning in this developmental period may be particularly critical as it may influence several major life transitions, such as moving out of

the parents' home, entering higher education or the work place, dating, sexual relationships, etc. (Laursen & Collins, 1994; Newman, Caspi, Moffitt, & Silva, 1997).

Second, we hypothesized that the association between parents' neuroticism and offspring interpersonal functioning would be partly mediated by offspring internalizing and externalizing problems in middle childhood. Based on previous studies, we expected that there would be significant continuity between the offspring's levels of internalizing and externalizing problems in childhood and their interpersonal functioning in adulthood (e.g., Broidy et al., 2003; Goodwin, Fergusson, & Horwood, 2004; Rutter, Kim-Cohen, & Maughan, 2006).

Third, given that the negative consequences of high neuroticism in parents on offspring are purportedly amplified in families having a parent with BD (Ellenbogen & Hodgins, 2004), and that there is a strong genetic association between affective disorders and neuroticism (Hettema, Neale, Myers, Prescott, & Kendler, 2006; Kendler et al., 2006a), we hypothesized that the association between parents' neuroticism and offspring's functioning in late adolescence-early adulthood would be stronger among the OBD than the OFH-. In addition, in order to determine whether the association between parents' personality and offspring functioning was specific to the trait of neuroticism, we examined the associations between parents' traits of extraversion, agreeableness, conscientiousness, and openness to experience and offspring's interpersonal functioning.

2.2 Method

Participants

The sample included 62 male and 62 female offspring, from 78 families, who were participating in an ongoing prospective study of families with a parent diagnosed with BD or parents with no mental disorder. Of the original sample, 18% of the OBD and 17% of the OFH- have refused to participate or have not been located as of August 2009. When offspring were between 4 and 12 years old, parents had rated their behaviour using the Child Behavior Checklist (CBCL; Achenbach, 1991). The CBCL ratings for offspring who did and who did not participate in the present wave of data collection were similar among both the OBD and OFH-. At baseline, the inclusion criteria for the study were: a) adults raising at least one biological child aged between 4 and 14 years; b) fluency in either English or French: and c) being raised and educated in Canada. Families in which either a parent or child had a chronic physical disease or handicap and/or an IQ below 70 were excluded. Parents with a diagnosis of BD, their spouses, and children were recruited from psychiatric outpatient clinics and from patient advocacy and support groups. All parents completed an interview with the Structured Clinical Interview for *DSM-III-R* (SCID-I; Spitzer, Williams, Gibbon, & First, 1992). Parents with BD reported, on average, symptoms 7.85 years (*SD* = 8.65 years) before the birth of the child included in the study. Families in which parents had no mental disorder were recruited in the same neighbourhoods as the families with BD, through physicians' offices and community organizations. None had a current Axis I disorder. Five parents of OFH- met criteria for a past drug use or anxiety disorder (for more information regarding the original sample, see Ellenbogen & Hodgins, 2004). Parents were mostly white, middle-class, and French speaking.

In the present follow-up study, the offspring ranged in age from 15 to 27 years (*M* = 19.81; *SD* = 3.01; see Table 1). Sixty-five offspring, from 44 families, had a parent with BD,

and 59 offspring, from 34 families, had parents with no mental disorder. Of the 44 families with BD, 20 families had a mother with BD and 24 families had a father with BD. In addition, 14 families had both a parent with BD and a parent with major depression. At the time of the present data collection, 35% of the offspring were living with both biological parents (14 OBD, 29 OFH-), 14% were living with one biological parent (16 OBD, 2 OFH-), 4% were living with one biological parent and a step-parent (4 OBD, 1 OFH-), 47% were living either alone, with a roommate or a partner (31 OBD, 27 OFH-), 93% were in school (59 OBD, 56 OFH-), and 52% were working (33 OBD, 32 OFH-).

Thirty-five offspring (22 OBD, 13 OFH-) met criteria for a current diagnosis according to *DSM-IV* (American Psychiatric Association, 1994). Current diagnoses included four affective disorders (3 OBD, 1 OFH-), 27 anxiety disorders (19 OBD, 8 OFH-), 15 substance-related disorders (10 OBD, 5 OFH-), and five other diagnoses (2 OBD with ADHD, 1 OBD with hypochondriasis, 1 OFH- with anorexia nervosa, and 1 OFH- with Tourette's Syndrome).

Measures

Time 1 (1995-1997; children aged 4-12 years old).

Revised NEO Personality Inventory (NEO-PI-R; Costa & McCrae, 1992b). Parents completed this self-report questionnaire that includes 240 items assessing the traits of neuroticism, extraversion, agreeableness, openness, and conscientiousness. High internal consistency, with coefficients ranging from .89 to .95, and temporal stability over six years have been reported (Costa, Herbst, McCrae, & Siegler, 2000; Rolland, Parker, & Stumpf,

1998). Studies have also demonstrated convergent and discriminant validity of the NEO-PI-R (Costa & McCrae, 1992b). Excellent psychometric proprieties have been demonstrated with the French translation (Rolland et al., 1998). For 115 offspring, the mean of both parents' scores for each of the five traits was used in the analyses, and for nine offspring, scores from one parent only were used[2].

Child Behavior Checklist (CBCL; Achenbach, 1991). Parents completed the parent report form (PRF) of the CBCL to assess internalizing and externalizing behaviours in their child. The CBCL PRF has good reliability and validity (Barkley, 1988). One-week and three-month test-retest reliabilities for externalizing problems were reported to be .95 and .84 respectively (Barkley, 1988). Concurrent validity has been established between the CBCL and other parent-reported behaviour scales and the Diagnostic Interview Schedule for Children (Barkley, 1988). CBCL scores were obtained for 103 offspring. For 95 offspring, the mean of ratings from two parents was used in the analyses, and for eight offspring, ratings from one parent were used.

Time 2 (2006-2008; children aged 15-27 years old).

UCLA Life Stress Interview (Adrian & Hammen, 1993; Hammen, 1991a). This semi-structured interview was developed to assess interpersonal and non-interpersonal functioning

[2] From a conceptual level, we view the use of *mean* parent personality scores as a more conservative and accurate approach to understanding the influence of parent's personality on offspring outcomes. In this way, the effects of one parent who is high on neuroticism can be offset by the buffering effects of a parent who is stable (i.e., low on the trait). Furthermore, from a statistical viewpoint, the use of data from multiple informants improves the distribution of data points, minimizes outliers, and therefore reduces the likelihood of spurious results.

in nine domains during the past six months. Functioning in each domain is coded on a five-point scale, using specific behavioural anchor points. Higher scores reflect poorer functioning. For example, in the social life domain, a score of 1 is described as "Exceptional social life - many good friends, very popular and engages in frequent social activities, gets along well with others, no conflict ", while a 5 is described as "Severe social problems with no friends, totally isolated from peers or frequent conflicts and fights, rejected by peers" (Hammen et al., 2003). Interpersonal functioning was defined as the sum of scores in the domains of close friends, social life, romantic relationships, and family relationships; non-interpersonal functioning was defined as the sum of scores in the domains of school, work, finances, health, and health of family members (Eberhart & Hammen, 2006; Hammen, Brennan, et al., 2004; Rudolph et al., 2000). Audio and/or video digital recordings of 14 interviews were rated independently by a second interviewer to estimate inter-rater reliability. Intraclass correlation coefficients revealed high reliability for all domains, with a mean of 0.82, similar to coefficients obtained in previous studies (Eberhart & Hammen, 2006; Hammen, Shih, et al., 2004; Shih, Eberhart, Hammen, & Brennan, 2006).

Diagnostic Interviews. The Structured Clinical Interview for DSM-IV (SCID-I; First, Gibbon, Spitzer, & Williams, 2002) is a semi-structured diagnostic interview designed to assess mental disorders. Many studies have shown the SCID-I to be a reliable and valid diagnostic instrument (e.g., Ramirez-Basco, Bostic, Davies, Rush, Witte, Hendickse et al., 2000; Zanarini & Frankenburg, 2001). The SCID-I was administered to offspring aged 19 or above (n = 77). For children aged 7 to 18 years old (n = 47), the Kiddie-Schedule for Affective Disorders and Schizophrenia- Present and Lifetime version (K-SADS-PL; Kaufman, Birmaher, Brent, & Rao, 1997) was used. It is highly reliable in children and

adolescents and considered to be an excellent interview for identifying affective disorders in youth (Kaufman et al., 1997; Kaufman, Schweder, Hilsenroth, & Segal, 2004). In the current follow-up study, both the SCID-I and K-SADS-PL were administered by experienced clinicians. Using audio and/or video digital recordings, 15 interviews (6 SCID-I and 9 K-SADS) were rated independently by a second clinician. Inter-rater reliability for diagnoses was high: kappa coefficients were 0.82, 0.71, and 1.0 for affective, anxiety, and substance use disorders respectively.

Procedure

At baseline, parents with BD and with no mental disorder were recruited in Montréal and surrounding regions. Following a telephone screening, parents completed the SCID-I interview, and a number of questionnaires including the Revised NEO Personality Inventory and CBCL PRF at home or at the university (see Ellenbogen & Hodgins, 2004 for full list of measures). Parents with BD were euthymic when completing questionnaires. Spouses were contacted and completed the same interviews and questionnaires, and offspring between the ages of 4 and 14 years were assessed.

When offspring reached late adolescence-early adulthood, they were contacted by telephone and invited to participate in the study. Offspring, and their guardian if they were 17 years or younger, provided written consent for participation in the study. They completed a diagnostic interview (SCID-I or Kiddie-SADS) and the UCLA Life Stress Interview conducted by a clinical psychologist. Offspring also completed questionnaires, underwent computer-based information processing tasks (data not reported here), and provided samples

of saliva at home. Participants received an honorarium of $150 CAN for participating in the current wave of data collection. All procedures were approved by the Human Research Ethics Committee of Concordia University.

Data analysis

Data were screened for outliers, defined as scores at least three standard deviations from the mean, and violations of normality. Scores for the nine domains of the chronic stress interview, as well as the aggregated mean scores, were positively skewed and therefore were log-10-transformed. All analyses were conducted on transformed data. However, to facilitate the interpretation of data, non-transformed data are presented in the text and tables.

Hierarchical multiple regressions were performed on the mean scores for interpersonal and non-interpersonal functioning separately. In both regressions, independent variables were entered in the following steps: (1) offspring age, offspring gender, and presence or absence of any current disorder in the offspring, (2) parents' neuroticism score. To determine whether the association between offspring functioning and parents' personality was specific to neuroticism, analyses examined parents' traits of extraversion, agreeableness, conscientiousness, and openness to experience as predictors of offspring interpersonal functioning.

Mediation analyses were conducted using Baron and Kenny's method (1986), which recommends testing mediation using three regression models. In step one, the independent variable must predict the dependent variable. In step two, the mediator must predict the dependent variable. In step three, when both the mediator and the independent variable are in

the regression equation, the initial association between the independent and dependent variables must be significantly reduced. These three steps were followed by the Sobel test, a more rigorous procedure to test for mediation (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002). A significant Sobel test suggests that the indirect effect of the independent variable on the dependent variable through the mediator is different from zero, and thus, that mediation is present. Finally, in order to examine whether a parental diagnosis of BD or offspring gender moderated the strength of the mediations, we conducted moderated mediation analyses, following recommendations outlined in Muller, Judd, and Yzerbyt (2005).

All analyses except the moderated mediations were conducted with and without siblings (using random deletion) to determine if the inclusion of siblings (i.e. non-independence) may have biased the results. Both sets of analyses yielded similar findings; we therefore included all participants in the analyses.

2.3 Results

Parents' neuroticism and offspring's functioning in late adolescence-early adulthood

As presented in Table 1, the OBD reported poorer interpersonal and non-interpersonal functioning than the OFH-. Correlations between scores for parents' personality traits and offspring's functioning in late adolescence-early adulthood and in childhood are presented in Table 2. The hierarchical multiple regression equation predicting offspring's interpersonal functioning was significant, accounting for 20.2% (R^2) of the variance (see Table 3, top panel). Parents' neuroticism scores accounted for 4.2% (change in R^2) of the variance in

interpersonal functioning in the offspring. In addition, the presence of a current mental disorder in the offspring was a significant predictor of interpersonal functioning, such that offspring with current mental disorders reported higher levels of interpersonal difficulties than those with no mental disorders. Gender was also a significant predictor, indicating that male offspring reported poorer interpersonal functioning than female offspring.

The regression equation predicting non-interpersonal functioning among offspring was significant and accounted for 14.2% (R^2) of the variance (see Table 3, bottom panel). In contrast to the results for interpersonal functioning, parents' neuroticism scores were not predictive of offspring's functioning in non-interpersonal domains. The presence of a current mental disorder in the offspring was a significant predictor of non-interpersonal functioning, such that offspring with mental disorders reported poorer functioning in non-interpersonal domains than non-disordered offspring. These results indicate that having a parent with high neuroticism is predictive of higher levels of interpersonal, but not non-interpersonal, difficulties, and that this association is independent of the well-known effects of current psychopathology on functioning.

Each of the above analyses was repeated after the random deletion of siblings within each family, so that there was only one sibling per family. The hierarchical multiple regression equation predicting interpersonal functioning among offspring was significant ($R = 0.51$, $F(4, 71) = 6.15$, $p < 0.001$). Parents' neuroticism scores ($\beta = 0.22$; $t = 2.09$, $p < 0.05$) and gender ($\beta = -0.26$; $t = -2.52$, $p < 0.05$) were significant predictors of interpersonal functioning. The regression equation predicting non-interpersonal functioning among offspring was significant ($R = 0.42$, $F(4, 71) = 3.80$, $p < 0.01$); parents' neuroticism scores were not predictive of offspring functioning in non-interpersonal domains ($\beta = 0.09$; $t = 0.81$,

ns). The results of these analyses indicate that the present findings were not influenced by the non-independence of data from offspring within the same families.

Other personality traits of parents and offspring's functioning in late adolescence-early adulthood

To determine if offspring's functioning in interpersonal and non-interpersonal domains was associated with other personality traits of their parents, similar analyses were undertaken. Parents' extraversion and openness to experience were not significant predictors of offspring's interpersonal or non-interpersonal functioning. Parents' levels of agreeableness ($\beta = -0.32$; $t = -3.54$, $p < 0.001$) and conscientiousness ($\beta = -0.23$; $t = -2.61$, $p < 0.01$) were negatively associated with offspring's functioning in interpersonal, but not non-interpersonal, domains.

Is the association between parents' personality and offspring functioning in late adolescence-early adulthood mediated by the offspring's childhood problem behaviours?

A series of multiple regressions were conducted to determine whether scores for internalizing and externalizing problems, measured when the offspring were between 4 and 12 years of age, mediated the associations between parents' personality traits and offspring's interpersonal functioning in late adolescence-early adulthood. The analyses included 103 participants for whom CBCL scores were available.

Parents' neuroticism was a significant predictor of offspring's interpersonal functioning ($\beta = 0.21$; $t = 2.47$, $p < 0.05$) and offspring's childhood internalizing scores ($\beta = 0.43$; $t = 4.97$, $p < 0.001$; see Figure 1, panel A). When scores for parents' neuroticism and offspring's childhood internalizing problems were both entered together into the regression

equation, childhood internalizing problems predicted offspring's interpersonal functioning later in life (β = 0.23; $t = 2.29$, $p < 0.05$), but parents' neuroticism was no longer a significant predictor of offspring's functioning (β = 0.18; $t = 1.90$, *ns*). According to Baron and Kenny (1986), these results suggest partial mediation of the association between parents' neuroticism and offspring's functioning by childhood internalizing problems. The results of the Sobel test, estimating whether the indirect effect is significantly different from zero, supported this view, but fell short of conventional statistical significance ($Z = 1.86$, $p = 0.063$).

Next, we examined whether offspring childhood externalizing scores mediated the association between parents' neuroticism and offspring's interpersonal functioning later in life. Parents' neuroticism predicted offspring's interpersonal functioning (β = 0.21; $t = 2.47$, $p < 0.05$) and offspring's childhood externalizing problems (β = 0.56; $t = 6.69$, $p < 0.001$; see Figure 1, panel B). When scores for parents' neuroticism and childhood externalizing problems were both entered into the regression equation, childhood externalizing problems predicted later offspring's interpersonal functioning (β = 0.31; $t = 3.03$, $p < 0.01$), while parents' neuroticism was no longer a significant predictor (β = 0.12; $t = 1.13$, *ns*). The Sobel test indicated that the mediation was significant ($Z = 2.73$, $p < 0.01$), meaning that the association between parents' neuroticism and offspring interpersonal functioning was partially mediated through childhood externalizing problems in offspring.

The statistical analyses were repeated after the random deletion of siblings within each family, so that there was only one sibling per family. Mediation analyses showed that parents' neuroticism was a significant predictor of offspring internalizing (β = 0.44; $t = 4.26$, $p < 0.001$) and externalizing scores (β = 0.55; $t = 5.32$, $p < 0.001$). When scores for parents'

neuroticism and childhood internalizing/externalizing problems were entered together into the regression equation, childhood internalizing problems (β = 0.27; $t = 2.12$, $p < 0.05$) and externalizing problems (β = 0.27; $t = 2.09$, $p < 0.05$) predicted interpersonal functioning later in life but parents' neuroticism was no longer a significant predictor of functioning in offspring. The results of these analyses indicate that the present findings were not influenced by the non-independence of data from offspring within the same families.

Since parents' traits of conscientiousness and agreeableness were negatively associated with offspring's interpersonal functioning, analyses were undertaken to determine if offspring's childhood problems mediated these associations. Parents' scores for conscientiousness did not predict childhood internalizing or externalizing scores (β = -0.07; $t = -0.74$, *ns* and β = -0.16; $t = -1.58$, *ns*, respectively), indicating that the association between parents' conscientiousness and offspring's interpersonal functioning is not mediated through childhood internalizing or externalizing problems in offspring.

Parents' agreeableness scores were associated with childhood internalizing (β = -0.30; $t = -3.36$, $p < 0.001$) and externalizing problems (β = -0.24; $t = -2.36$, $p < 0.05$) in offspring. When scores for parents' agreeableness and offspring's childhood internalizing problems were entered together into the regression equation, childhood internalizing problems predicted later interpersonal functioning in offspring (β = 0.35; $t = 3.74$, $p < 0.001$), but parents' agreeableness was no longer a significant predictor of interpersonal functioning in offspring (β = -0.16; $t = -1.75$, *ns*). The Sobel test indicated that the mediation was not significant ($Z = -1.69$, *ns*). Mediation analyses were then conducted for externalizing problems in childhood. When scores for parents' agreeableness and childhood externalizing problems in offspring were both entered into the regression equation, offspring's childhood

externalizing problems predicted later interpersonal functioning in offspring (β = 0.36; t = 4.04, $p < 0.001$), but parents' agreeableness was no longer a significant predictor (β = -0.14; t = -1.54, *ns*). The Sobel test indicated that the mediation was significant (Z = -2.00, $p < 0.05$), meaning that the association between parents' agreeableness and offspring's interpersonal functioning was partially mediated through the offspring's externalizing behaviours in middle childhood.

Is the association between parents' personality and offspring functioning in late adolescence-early adulthood mediated by the offspring's childhood social competence?

In order to verify whether the association between parents' neuroticism and offspring's functioning in late adolescence-early adulthood was associated with the offspring's social competence in childhood, further mediation analyses were undertaken using the social relations competence scale of the CBCL's parent-report form. Parents' neuroticism was not a significant predictor of social competence assessed when the offspring were children (β = -0.01; t = -0.09, *ns*). When scores for parents' neuroticism and social competence were entered together into the regression equation, parents' neuroticism predicted offspring interpersonal functioning in late adolescence-early adulthood (β = 0.21; t = 2.46, $p < 0.05$), but social competence was not a significant predictor (β = -0.05; t = -0.55, *ns*). Overall, these analyses suggest that social competence in childhood does not mediate the association between parents' neuroticism and offspring interpersonal functioning in late adolescence-early adulthood.

Does parents' bipolar disorder moderate the observed mediations?

We examined whether a parental diagnosis of BD moderated the strength of the mediated associations that were found between parents' personality and offspring's interpersonal functioning in late adolescence-early adulthood. To accomplish this, we conducted exploratory regression analyses to test for moderated mediation (see Table 4). In the first step of the analyses, we included offspring's age, gender, and current diagnosis as control variables. In the second step, we included parents' neuroticism, parent BD (present or absent), and the mediator when appropriate. In the third step, we included the interaction terms.

We first examined whether parents' BD moderated the mediation of offspring's childhood internalizing problems on the association between parents' neuroticism and offspring's interpersonal functioning in late adolescence-early adulthood. The first equation showed that the interaction between parents' neuroticism and parent BD did not predict offspring interpersonal functioning, suggesting that the effect of parents' neuroticism on later functioning in offspring is not moderated by the presence of BD in parents (see Table 4, top panel). The second equation showed that parents' BD was a significant moderator. The association between parents' neuroticism and offspring's internalizing problems in childhood was significantly stronger among the OBD than the OFH-. Childhood internalizing problems, however, predicted interpersonal functioning equally among all offspring. Given the small sample size and the absence of association between neuroticism and offspring's interpersonal functioning in the first set of equations, these results should be interpreted cautiously.

We then examined whether parents' BD moderated the mediation of offspring's childhood externalizing problems on the association between parents' neuroticism and offspring's interpersonal functioning in late adolescence-early adulthood. No moderation of the mediation by parents' BD was detected (see Table 4, bottom panel).

An analysis was undertaken to examine whether the presence of BD among the parents moderated the mediation by offspring's childhood externalizing problems of the association between parents' agreeableness and later interpersonal functioning in offspring. No interaction terms were significant, suggesting that parents' BD did not moderate the mediation.

Does offspring gender moderate the observed mediations?

Finally, we were interested in examining whether offspring gender moderated the strength of the mediated associations that were found between parents' personality traits and offspring's interpersonal functioning in late adolescence-early adulthood. We thus conducted exploratory regression analyses to test for moderated mediation, as described in the previous section. Overall, gender did not moderate any of the associations found between parental neuroticism, CBCL scores, and interpersonal functioning.

2.4 Discussion

In this prospective 10-year study of youth at high and low risk for affective disorders, we examined the associations between parents' personality traits, offspring's internalizing and

externalizing problems in middle childhood, and offspring's interpersonal functioning in late adolescence-early adulthood. Three hypotheses were tested. First, the hypothesis that parents' neuroticism would predict interpersonal functioning in offspring was supported, even after controlling for the offspring's age, gender, and current disorders. Although a few studies have examined the association between parents' neuroticism and child psychosocial outcomes (Degnan, Henderson, Fox, & Rubin, 2008; Kochanska et al., 1997; Sullivan, 1997), the present investigation is the first, to our knowledge, to report that parents' personality may have a long-term influence on interpersonal functioning in offspring. Conversely, parents' neuroticism did not predict offspring's functioning in non-interpersonal domains such as school, work, finances, and health habits. Thus, parents' neuroticism specifically influenced offspring's functioning in interpersonal domains in late adolescence-early adulthood.

Our second hypothesis was that the association between parents' neuroticism and interpersonal functioning in offspring would be mediated in part by offspring's childhood internalizing and externalizing problems. While the hypothesis was supported, the mediation through childhood internalizing problems was modest while that of externalizing problems was stronger. The finding of an association between parents' neuroticism and childhood problems in offspring is consistent with results from our previous cross-sectional study undertaken when the offspring were children (Ellenbogen & Hodgins, 2004) and from other studies (Kochanska et al., 1997; Kurdek, 2003). The present study extends these previous findings by showing that offspring's problems in middle childhood are associated with poor interpersonal functioning 10 years later. These results are in line with evidence showing that internalizing and externalizing problems in childhood exhibit continuity over time and increase the risk of similar difficulties and mental disorders in early adulthood (Broidy et al.,

2003; Caspi, Moffitt, Newman, & Silva, 1996; Goodwin et al., 2004; Shiner, Masten, & Roberts, 2003). Thus, childhood problems in offspring mediated the association of parents' neuroticism and offspring's interpersonal functioning in late adolescence-early adulthood.

Our third hypothesis, that parents' neuroticism would be more strongly associated with interpersonal functioning among the OBD than the OFH-, and that the mediation of offspring childhood problems would be stronger in high-risk than low-risk families, was partially supported. Despite the small sample size, the diagnosis of BD in parents moderated the association between parents' neuroticism and childhood internalizing problems among offspring, but not the association between childhood internalizing problems and interpersonal functioning a decade later. In other words, offspring whose parents had both high neuroticism scores and a diagnosis of BD were more likely to have presented internalizing problems in middle childhood than the offspring of parents with either BD or high neuroticism alone. Internalizing problems in middle childhood increased the risk for poor interpersonal functioning 10 years later, regardless of the presence of BD among the parents. These data support recent evidence highlighting the importance of anxiety in childhood as a precursor to the development of an affective disorder among offspring of parents having BD (Duffy et al., 2010; Goldstein et al., 2010). In sum, the results suggest a pattern of relative continuity across generations in families having a parent with BD, but not in non-affected families, defined by a trajectory of high emotionality in parents, offspring internalizing problems in childhood, and interpersonal dysfunction in late adolescence and early adulthood.

Few studies have examined the association between parents' neuroticism and offspring outcomes among parents with a mental disorder. The few studies that have

addressed this issue have, for the most part, been cross-sectional and focused on infancy and childhood (Brook, Whiteman, & Zheng, 2002; Ellenbogen & Hodgins, 2004; Sullivan, 1997). Furthermore, differences in the measures of parents' personality traits and outcomes among offspring make it difficult to compare the results of these studies. The paucity of research on offspring of parents with mental disorders might stem from the challenge of distinguishing personality and symptomatology. Several models have been posited to explain the associations between personality traits, especially neuroticism, and affective disorders (for review, see Klein, Durbin, Shankman, & Santiago, 2002). Overall, the extant literature suggests that neuroticism is a stable trait (Costa et al., 2000) that contributes to the development of affective disorders (Fanous, Neale, Aggen, & Kendler, 2007).

While the present study focused on the trait of neuroticism because it is strongly associated with affective disorders (Bagby, Bindseil, Schuller, & Rector, 1997; Kendler, Kuhn, & Prescott, 2004; Widiger & Trull, 1992), analyses were conducted to determine if other personality traits of the parents were associated with functioning among offspring. Parents' traits of conscientiousness and agreeableness, but not extraversion and openness to experience, were both negatively associated with interpersonal difficulties among offspring in late adolescence-early adulthood. Agreeableness is a tendency to be compassionate, kind, and cooperative; conscientiousness is the tendency to aim for achievement and to be self-disciplined and hard-working (Costa & McCrae, 1992a). Low agreeableness in parents, but not low conscientiousness, predicted more externalizing problems among the offspring in middle childhood, which in turn, predicted poor interpersonal functioning 10 years later. Thus, parents' traits of agreeableness and neuroticism were associated with offspring externalizing problems in middle childhood and interpersonal functioning among offspring

later in life. By contrast, only the parental trait of neuroticism was associated with internalizing behaviours among offspring in middle childhood. Given that the traits of neuroticism, agreeableness, and conscientiousness are independent of each other (Costa et al., 2000; Costa & McCrae, 1992b), the associations between these traits in parents and their offspring's interpersonal functioning in late adolescence-early adulthood may reflect different developmental trajectories leading to the same outcome, a concept known as "equifinality" (Cicchetti & Toth, 1995). The association between high neuroticism in parents and offspring internalizing problems in middle childhood and poor interpersonal functioning in late adolescence-early adulthood is consistent with findings from studies of the offspring of parents with major depression, which show evidence of an intergenerational transmission of internalizing problems (Hammen, Shih, et al., 2004; Rutter, 2004; Weissman, Wickramaratne, et al., 2006). Thus, poor interpersonal functioning among offspring in late adolescence-early adulthood may signal an increased risk for major depression. By contrast, the association between parents' high neuroticism and low agreeableness and offspring externalizing problems in middle childhood may represent a different pathway to poor interpersonal functioning among offspring in late adolescence-early adulthood. High neuroticism and low agreeableness both contribute to trait anger, with the former being associated with angry affect and the latter with the control of aggressive responses (Martin, Watson, & Wan, 2000). Perhaps, this developmental trajectory incorporates the transmission of anger and reactive aggression from parents to offspring, reflected in the externalizing problems in middle childhood and impaired interpersonal functioning in late adolescence-early adulthood. In a similar fashion, maternal negativity in childhood predicted poor executive functioning and the subsequent development of BD in young adulthood among the

offspring of parents with an affective disorder (Meyer et al., 2006). Thus, parental agreeableness may highlight a unique developmental trajectory to poor interpersonal functioning and psychopathology in late adolescence-early adulthood.

At least three, not mutually exclusive mechanisms of transmission could account for the associations observed between parents' personality traits and outcomes among offspring. First, genes may partly explain the observed associations. There is evidence that the big five personality traits are determined, in part, by genetic factors (Bouchard & Loehlin, 2001; Loehlin, 1992). In addition, levels of neuroticism are elevated in the healthy first-degree relatives of people with major depression (Maier, Minges, Lichtermann, Franke, & Gansicke, 1995), suggesting that one facet of the genetic vulnerability for affective disorders may be expressed as the trait of neuroticism. Indeed, biometric modelling studies of twin populations have suggested that the same genes contribute to neuroticism and depression (Fanous, Gardner, Prescott, Cancro, & Kendler, 2002; Hettema et al., 2006; Kendler et al., 2006a). Therefore, a child who inherits the genes associated with affective disorders may also inherit a tendency to react emotionally to stressors and daily problems (van Os & Jones, 1999), which in turn, might impede the development of interpersonal skills and meaningful interpersonal relationships. Although less is known about the association between agreeableness and affective disorders (Meyer et al., 2006), one study reported that patients with BD have low levels of this trait (Lozano & Johnson, 2001) and other studies have shown that low levels of agreeableness in adolescents were associated with externalizing problems (Miller, Lynam, & Jones, 2008; Pursell, Laursen, Rubin, Booth-Laforce, & Rose-Krasnor, 2008). Thus, the child who inherits genes associated with low agreeableness may

exhibit externalizing problems that in turn would increase rejection by peers and social dysfunction.

A second mechanism by which parents' personality may affect offspring outcomes is modelling. Individuals high in neuroticism experience a host of negative emotions, generate stressful life events, and exhibit poor skills for coping with stress (Belsky & Barends, 2002; DeLongis & Holtzman, 2005; Ellenbogen & Hodgins, 2004; Watson et al., 2005). Likewise, individuals low on agreeableness tend to be angry, manipulative and competitive, and to resolve conflicts using coercive tactics (Jensen-Campbell & Graziano, 2001; Kuppens, 2005). Thus, parents with high levels of neuroticism and low levels of agreeableness may model maladaptive and dysfunctional behaviours that influence their offspring's social development and abilities for coping with stress (Brook et al., 2002; Compas, Connor-Smith, & Jaser, 2004; Degnan et al., 2008; Ellenbogen & Hodgins, 2004). The offspring's difficulties may further enhance their vulnerability for affective disorders.

Third, as has been suggested in Belsky's process model of parenting (1984), the association between parents' personality and offspring outcomes may result from poor parenting practices and disruptions in the parent-child relationship. High neuroticism in parents, relative to low neuroticism, has been associated with a parenting style that is less warm and responsive, and more inconsistent, disorganized, and intrusive (Belsky et al., 1995; Clark et al., 2000; Ellenbogen & Hodgins, 2004; Kochanska et al., 1997). Few studies have examined the association between agreeableness and parenting style, but those that have found high agreeableness to predict positive affect and less controlling behaviours (Belsky et al., 1995; Losoya, Callor, Rowe, & Goldsmith, 1997), and low agreeableness to predict less responsive parenting (Clark et al., 2000; Kochanska et al., 1997). Thus, parents' personality

and the associated parenting behaviours may negatively affect family functioning and parent-child interactions, which in turn, increase the likelihood of problem behaviours and poor interpersonal functioning in the offspring similar to those presented by their parents (Elder et al., 1986).

Among adolescents and young adults, deficits in interpersonal functioning are associated with the development of major depression (Davila, Hammen, Burge, Paley, & Daley, 1995; Eberhart & Hammen, 2006; Hammen, Shih, et al., 2004). Consequently, understanding the mechanisms leading to poor psychosocial functioning will contribute to clarifying the etiology of depression. Individuals presenting poor interpersonal functioning have difficulty establishing and maintaining relationships with friends, colleagues, romantic partners, and family members. They often suffer from loneliness, lack social support, and demonstrate poor skills in resolving conflicts (Cattan, Newell, Bond, & White, 2003; Eberhart & Hammen, 2006; Hammen, Shih, et al., 2004; Heinrich & Gullone, 2006). An understanding of the mechanisms involved in the emergence of affective disorders is essential to establishing successful prevention programs, especially in children at elevated genetic risk for these disorders (Beardslee & Gladstone, 2001; Garber et al., 2009). Evidence from the present study suggests that interpersonal functioning may be a relevant target for such interventions among high-risk children before behavioural problems emerge.

The finding that parents' level of neuroticism was more strongly predictive of offspring internalizing problems in middle childhood among families with a parent having BD, relative to families with no affective disorders, suggests that the OBD are more sensitive to the consequences of their parents' high levels of neuroticism than the OFH-. It is reasonable to assume that the sub-group of OBD who will develop major affective disorders

in adulthood will have inherited a tendency for high levels of neuroticism (Kendler et al., 2006a; Kendler et al., 2004). This tendency to over-react – behaviourally and emotionally – would make these offspring more sensitive to the negative consequences of their parents' high levels of neuroticism such as creating a chaotic, unstructured, and stressful family environment (Chang et al., 2001; Ellenbogen & Hodgins, 2004; Romero et al., 2005). This family environment, coupled with parental modeling of inadequate skills for coping with stress, may lead to the internalizing problems (Birmaher et al., 2010; Giles et al., 2007) and HPA hyperactivity (Ellenbogen & Hodgins, 2009; Ellenbogen et al., 2010) that has been observed among the OBD in childhood and adolescence. Increased childhood internalizing problems, in turn, increase the risk of poor interpersonal functioning in late adolescence-early adulthood, which ultimately increases the risk of developing an affective disorder (Hammen et al., 2003). Thus, these hypothesized environmental mechanisms, compounded by changes to the HPA axis, may enhance an inherited predisposition among the sub-group of offspring who will later develop affective disorders to react emotionally to stressors and daily hassles from an early age.

The strengths of this study include an inter-generational longitudinal design, a unique sample of parents with BD and their offspring, diagnostic interviews conducted on all parents and offspring, and high interrater reliability for diagnoses and for ratings of offspring functioning in late adolescence-early adulthood. Some limitations of the study warrant discussion. The sample may not have been large enough to detect effect sizes of small magnitude, and therefore negative findings should be interpreted with caution. Caution should also be used when interpreting borderline significant results and the moderated mediation analyses. Moreover, the inclusion of siblings transgresses the independence of

cases assumption. The findings were replicated, however, in a sub-sample that included only one child per family, suggesting that the present results are not due to alpha inflation associated with the non-independent data. It is also possible that the results may be confounded by a reporting bias; parents reported on their own personality and offspring's behavioural problems. Studies of reporting biases associated with affective disorders have been inconclusive, with some studies showing bias (e.g., Weisz, Rudolph, Granger, & Sweeney, 1992) and others no bias (e.g., Richters, 1992). To attempt to counter any such possible bias, parents completed both measures when euthymic and mean scores from two parents for both their own personality and their child's behaviour were used in the majority of cases. No reporting bias was associated with the outcome measure, offspring's interpersonal functioning in late adolescence-early adulthood. It is also possible that a variable not measured in the study was responsible for the present results. As the study focused on the offspring of parents with BD, the extent to which the results generalize to other samples can only be determined by future research. Finally, the offspring ranged in age from 15 to 27 years old. While there were no significant differences on scores for functioning in any of the interpersonal domains between the offspring aged 15-18 years (n = 47) and those aged 19-27 years (n = 77), the younger offspring presented more problems at school [$F(1, 110) = 4.85$; $p < 0.05$] and fewer financial problems [$F(1, 122) = 8.48$; $p < 0.01$] than the older offspring.

To conclude, the present study showed that parents' personality traits may be associated with the initiation of a maladaptive developmental trajectory towards affective disorders among some of their offspring. Future work in this area should focus on understanding the mechanisms at play, such as the role of specific genetic polymorphisms

associated with affective disorders (Gotlib, Joormann, Minor, & Hallmayer, 2008) and gene-environment interplay (Rutter, Moffitt, et al., 2006; Taylor et al., 2006). In the meantime, the present study has shown that high levels of neuroticism and low levels of agreeableness among parents predict poor interpersonal functioning among their offspring in late adolescence-early adulthood, that these associations are mediated by offspring's internalizing and externalizing problems in middle childhood, and that the mediation may be stronger in families in which a parent has BD.

Table 1: Parent and offspring variables.

	OBD	OFH-	Total	*F*[a]
N	65	59	124	
Gender (Male:Female)	35:30	27:32	62:62	
TIME 1 (1995-1997)				
Offspring mean age (years) ± SD	8.43 ± 2.51	7.67 ± 2.36	8.06 ± 2.45	3.02
Offspring mean CBCL internalizing t score ± SD	52.97 ± 9.99	47.75 ± 7.59	50.49 ± 9.27	8.41**
Offspring mean CBCL externalizing t score ± SD	53.24 ± 10.69	44.61 ± 9.17	49.14 ± 10.85	17.93***
Parents' mean neuroticism t score ± SD	53.24 ± 7.56	45.99 ± 5.69	49.75 ± 7.61	33.48***
TIME 2 (2006-2008)				
Offspring mean age (years) ± *SD*	20.26 ± 3.19	19.31 ± 2.74	19.81 ± 3.01	3.76
Offspring mean interpersonal functioning[b] ± SD	2.17 ± 0.52	1.89 ± 0.35	2.04 ± 0.47	13.76***
Offspring mean non-interpersonal functioning[b] ± SD	2.33 ± 0.47	1.99 ± 0.32	2.17 ± 0.44	20.24***

OBD: Offspring of parents with bipolar disorder; OFH-: Offspring without a family history of BD.

[a] Main effect of group (difference between the bipolar and no mental disorder families).

[b] Higher scores represent worse functioning in interpersonal and non-interpersonal domains, rated on a 5-point scale.

**$p < 0.01$; *** $p < 0.001$.

Table 2: Correlations among parents' and offspring's variables.

	1	2	3	4	5	6	7
1. Parents' neuroticism	-						
2. Parents' agreeableness	-0.32**	-					
3. Parents' conscientiousness	-0.36**	0.42**	-				
4. Offspring interpersonal functioning	0.23*	-0.24*	-0.16	-			
5. Offspring non-interpersonal functioning	0.26**	0.02	-0.03	0.41**	-		
6. Offspring childhood internalizing problems	0.44**	-0.18	-0.07	0.41**	0.16	-	
7. Offspring childhood externalizing problems	0.55**	-0.21*	-0.15	0.41**	0.36**	0.68**	-

* $p < 0.05$; ** $p < 0.01$.

Table 3: Parents' level of neuroticism as predictor of offspring outcomes: Results of a hierarchical multiple regression analysis.

Predictors	Offspring interpersonal functioning in late adolescence-early adulthood						
	r	Partial *r*	β	*t*	*R*	Adj. R^2	Δ*F*
Step 1							
Age	0.13	0.06	0.06	0.69			
Gender	-0.21	-0.25	-0.24	-2.78**			
Offspring current disorder	0.32	0.33	0.33	3.75***			
Total step					0.40	0.14	7.52***
Step 2							
Age		0.07	0.07	0.79			
Gender		-0.22	-0.21	-2.45*			
Offspring current disorder		0.29	0.28	3.25**			
Parents' neuroticism	0.29	0.22	0.21	2.47*			
Total step					0.45	0.18	6.09*
	Offspring non-interpersonal functioning in late adolescence-early adulthood						
Step 1							
Age	0.16	0.10	0.10	1.91			
Gender	-0.13	-0.16	-0.15	-1.75			
Offspring current disorder	0.30	0.28	0.29	3.20**			
Total step					0.35	0.96	5.30**
Step 2							
Age		0.11	0.11	1.91			
Gender		-0.14	-0.13	-1.48			
Offspring current disorder		0.30	0.25	2.80**			
Parents' neuroticism	0.22	0.16	0.16	1.79			
Total step					0.38	0.11	3.12***

Note: $n = 122$; adj. R^2 = adjusted R^2; partial *r* = partial correlation.

*$p < 0.05$; **$p < 0.01$; *** $p < 0.001$.

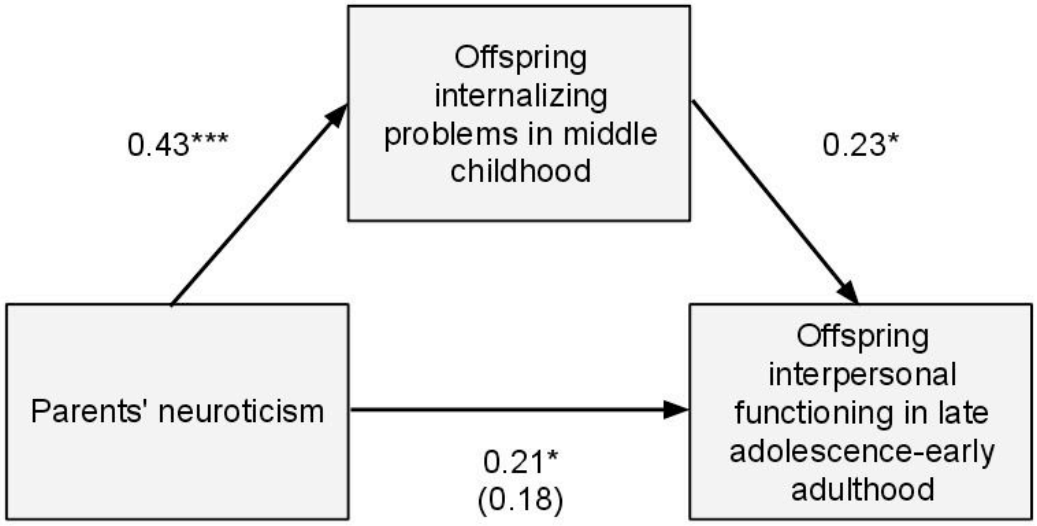
Table 4: Results of regression models estimating moderated mediation with internalizing problems (top) and externalizing problems (bottom).

	Equation 1			**Equation 2**			**Equation 3**		
	Criterion: offspring interpersonal functioning			**Criterion: offspring childhood CBCL scores**			**Criterion: offspring interpersonal functioning**		
Predictors	β	*t*	*p*	β	*t*	*p*	β	*t*	*p*
	Moderated mediation through internalizing problems								
Parents' neuroticism	0.12	1.20	*ns*	0.32	3.01	<.01	0.10	0.88	*ns*
Parent BD	0.20	2.11	<.05	0.12	1.20	*ns*	0.18	1.75	*ns*
Parents' neuroticism × Parent BD	-0.03	-0.29	*ns*	**0.19**	**1.97**	**<.05**	-0.02	-0.15	*ns*
Offspring internalizing score							0.20	1.96	.053
Parent BD × Offspring internalizing score							0.07	0.66	*ns*
	Moderated mediation through externalizing problems								
Parents' neuroticism	0.12	1.20	*ns*	0.44	4.32	<.001	0.05	0.44	*ns*
Parent BD	0.20	2.11	<.05	0.19	1.92	.058	0.15	1.50	*ns*
Parents' neuroticism × Parent BD	-0.03	-0.29	*ns*	0.06	0.65	*ns*	0.00	-0.03	*ns*
Offspring externalizing score							0.27	2.57	<.05
Parent BD × Offspring externalizing score							0.07	0.74	*ns*

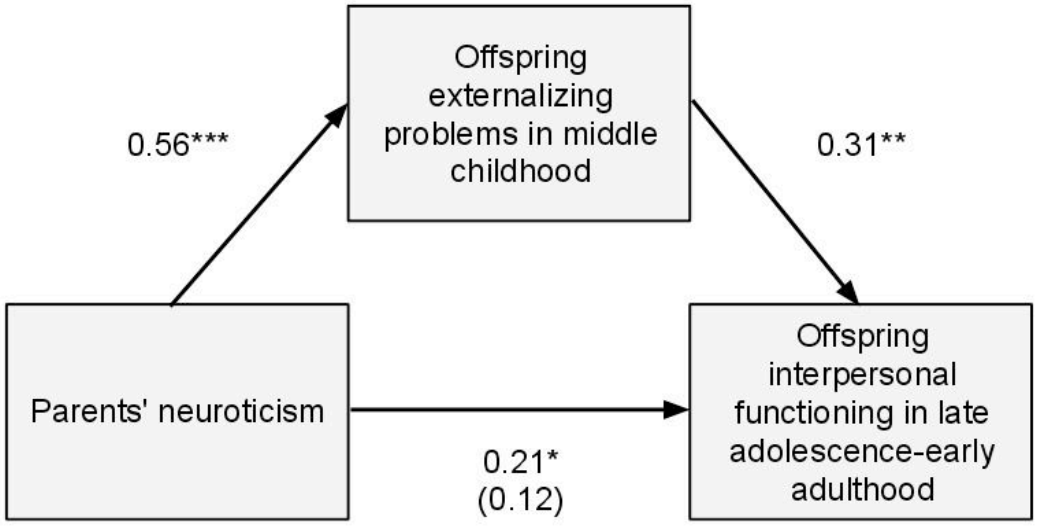
Note: BD = bipolar disorder diagnosis, CBCL = Child Behavior Checklist. Multiplied terms represent interactions.

Figure 1: Standardized regression coefficients for the mediation models.

A



B



Standardized regression coefficients for the mediation models. Panel A depicts a partial mediation, with internalizing problems as the mediator. Panel B depicts a partial mediation through externalizing problems. The numbers in parentheses are the coefficients of the association between parents' neuroticism and offspring functioning when the mediator is in the regression equation. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

3. TRANSITION TO MANUSCRIPT 2

3.1 Hypothalamic-pituitary-adrenal (HPA) axis

The HPA axis plays a major role in the endocrine system, regulating glucose metabolism, the immune system, alterations in blood flow as well as the stress response (McEwen, 2000). The HPA axis is responsible for a cascade of endocrine events beginning in the hypothalamus, with the release of corticotrophin-releasing hormone (CRH). CRH travels to the anterior pituitary gland via the hypophyseal portal system, provoking the release of adrenocorticotropic hormone (ACTH). In turn, ACTH leaves the brain and travels to the cortex of the adrenal glands, where glucocorticoids (cortisol in humans) are produced and released into circulation. The HPA axis is also characterized by a negative feedback loop; cortisol can travel back to the brain, bind to glucocorticoid receptors, and suppress the endocrine cascade, therefore reducing the output of hormones. Additionally, glucocorticoid receptors can act as transcription factors and elicit changes in gene expression that prepare the organism for future challenges (de Kloet, Karst, & Joels, 2008; Sapolsky, Romero, & Munck, 2000).

Although the HPA system is activated in response to internal and external challenges, it follows a relatively stable diurnal pattern that has implications for health. Under normal conditions, the HPA axis follows a circadian rhythm, with a peak of cortisol release after awakening (Edwards, Clow, Evans, & Hucklebridge, 2001; Wüst, Wolf, et al., 2000), and a steady decrease in cortisol concentration throughout the day.

The awakening cortisol response is a sharp rise and fall of cortisol levels in the 45 to 60 minutes immediately following awakening (Clow, Thorn, Evans, & Hucklebridge, 2004). It has been shown to be consistent from day to day, and it is not influenced by sleep characteristics (e.g., duration, quality, etc.; for review see Clow et al., 2004), except for time of awakening (Stalder, Evans, Hucklebridge, & Clow, 2010). Furthermore, the awakening response seems to be uncorrelated to diurnal cortisol concentrations (Edwards et al., 2001), which suggests that regulatory mechanisms as well as physiological consequences of the awakening and diurnal cortisol might differ. Studies indicate that the awakening response is determined, in part, by genetic factors, but not diurnal activity (Kupper et al., 2005; Wüst, Federenko, Hellhammer, & Kirschbaum, 2000).

The functions of the awakening cortisol response are still not well understood (Fries, Dettenborn, & Kirschbaum, 2009). It was initially thought to mobilize glucose to prepare the body for the day's demands, but research has now shown that this is not the case (Hucklebridge, Clow, Abeyguneratne, Huezo-Diaz, & Evans, 1999). It was also hypothesized that it might be involved in regulating the immune system (Petrovsky & Harrison, 1997), but this theory needs to be investigated further. Although much research has been devoted to elucidating the negative impact of hypercortisolemia, few studies have focused specifically on the impact of high awakening cortisol levels. There is some evidence for the awakening response to be implicated in perceived stress, burnout, and non-clinical depression (De Vente, Olff, Van Amsterdam, Kamphuis, & Emmelkamp, 2003; Pruessner, Hellhammer, Pruessner, & Lupien, 2003; Schulz, Kirschbaum, Prussner, & Hellhammer, 1998; Stalder et al., 2010; Steptoe, Cropley, Griffith, & Kirschbaum, 2000).

3.2 Allostasis and allostatic load

McEwen (2003) proposed a theoretical model to explain the link between the HPA axis, stress, and illness (including psychopathology). In order to adapt to changes in the environment, physiological systems are upheld via allostasis, that is, maintaining "stability through change" (McEwen, 2004, p.1). In response to everyday stressors, the HPA axis, combined with other autonomic, immune and endocrine systems, is activated to promote normal adaptation. This process is adaptive and beneficial, but can become detrimental under certain conditions. For instance, when the HPA axis is activated unnecessarily or when it does not properly shut down, the consequences can be deleterious on the brain and body, via cumulative costs on different biological systems, which is referred to as allostatic load. Chronic hypercortisolemia is believed to represent an example of allostatic load, because it is associated with adverse consequences such as increased abdominal obesity, type 2 diabetes, osteoporosis, immunosuppression, hypertension, cardiovascular disease, depressive affect, and memory loss (Brown, Varghese, & McEwen, 2004; Epel et al., 2000; Lupien, McEwen, Gunnar, & Heim, 2009; McEwen, 2000; Sapolsky et al., 2000; Starkman, Giordani, Berent, Schork, & Schteingart, 2001). It is thus possible that allostatic load may be one biological mechanism responsible for the association between stress and psychopathology.

3.3 The HPA axis and affective disorders

The link between stress and major depression is well established; studies have now shown that both acute and chronic stress play a role in the onset, maintenance, and recurrence of

episodes (Mazure, 1998; McGonagle & Kessler, 1990). However, the mechanisms linking stress and depression are not well understood. One possibility is that the HPA axis dysregulation acts as a mediator between stress and the affective disorders.

Many studies have now shown that depressed individuals exhibit distinct HPA parameters compared to healthy controls (for review, see Stetler & Miller, 2011). Across multiple studies, major depression has been associated with an overproduction of CRH (Nemeroff et al., 1984), reduced function of glucocorticoid receptors (Pariante & Miller, 2001), hypercortisolemia (Deuschle et al., 1997), increased and blunted cortisol levels at awakening (Bhagwagar, Hafizi, & Cowen, 2005; Stetler & Miller, 2005; Taylor, Glover, Marks, & Kammerer, 2009), and an abnormal response to the dexamethasone suppression test (Fountoulakis, Gonda, Rihmer, Fokas, & Iacovides, 2008) and the combined dexamethasone/CRH test (Rybakowski & Twardowska, 1999; Schmider et al., 1995). A recent meta-analysis examined 20 studies of depressed participants and concluded that depressed persons have higher salivary cortisol in the morning and evening than controls; the authors do state, however, that this group difference was small and that a large heterogeneity existed between the studies (assay kits, severity of depression, etc.; Knorr, Vinberg, Kessing, & Wetterslev, 2010). Unfortunately, most studies to date have been cross-sectional and could not examine whether HPA dysregulations precede the onset of depression, whether they are a consequence (scar) of the disorder, or whether they are a state-dependent marker. Some studies have shown that remitted patients have elevated cortisol levels, suggesting that high cortisol may represent a putative risk factor for future episodes, rather than a marker of a current depressive episode (Bhagwagar, Hafizi, & Cowen, 2003; Bhagwagar et al., 2005; Zobel et al., 2001).

Similarly to studies of depression, studies suggest that individuals with BD exhibit distinct HPA parameters compared to healthy controls; however the results are more mixed than with depression. Overall, studies have shown elevated (Deshauer et al., 2003) and normal waking cortisol levels (Deshauer, Duffy, Meaney, Sharma, & Grof, 2006), elevated serum cortisol levels over 24 hours (Cervantes, Gelber, Kin, Nair, & Schwartz, 2001), elevated nocturnal cortisol levels (Linkowski et al., 1994), and an abnormal response to the dexamethasone suppression test (Rush et al., 1997) and the dexamethasone/CRH test (Schmider et al., 1995; Watson, Gallagher, Ritchie, Ferrier, & Young, 2004). To date, the literature suggests that the HPA axis is functioning abnormally in individuals with BD, similarly to what has been observed in depressed individuals; however, there is little evidence of elevated cortisol in this population (see Deshauer et al., 2006). Furthermore, possible moderators of HPA function (e.g., type of episode, remission, medication, etc.) are not well understood.

3.3.1 HPA research in high-risk samples

Studies of the HPA axis in the offspring of parents with depression is limited compared to studies of individuals diagnosed with depression, Overall, the results are mixed, with some studies showing HPA axis dysfunctions in high-risk participants (Field et al., 1988; Lundy et al., 1999; Mannie et al., 2007) and other studies showing no difference between high- and low-risk participants (Ashman, Dawson, Panagiotides, Yamada, & Wilkinson, 2002; Ising, Lauer, Holsboer, & Modell, 2005; Ronsaville et al., 2006). More importantly, prospective studies have reported a relationship between cortisol levels and depression (Harris et al.,

2000). One study showed that high morning cortisol levels at 13 years of age in the offspring of depressed mothers predicted depressive symptoms at age 16, even after controlling for symptoms at age 13 (Halligan, Murray, Martins, & Cooper, 2007). Goodyer et al. (2009) found that in adolescents with the high-risk genotype (at least one short allele in the promoter region of the serotonin transporter gene [5-HTTLPR]), high waking cortisol levels predicted depressive episodes 12 months later. Adolescents with the low-risk genotype did not show this association between morning cortisol and depressive episodes. Finally, in a prospective study of adult women at high risk for depression on the basis of psychosocial factors, morning cortisol levels measured at 8AM predicted the onset of a depressive episode over the next 12 months (Harris et al., 2000).

In the OBD, Deshauer et al. (2006) found that adolescent and adult offspring (range 16 to 33 years) with a history of depression, but who were not currently depressed, showed no HPA axis dysfunction. On the other hand, participants from the sample of OBD described in this thesis have consistently exhibited higher daytime saliva cortisol levels in adolescence and young adulthood compared to offspring of parents with no mental disorders (Ellenbogen, Hodgins, & Walker, 2004; Ellenbogen et al., 2006; Ellenbogen et al., 2010). In the most recent study, cortisol measured in the afternoon over 14 days was higher among the OBD than the control participants; the cortisol difference was not related to the small number of participants with diagnoses of mental disorders, nor was it associated with self-reports or parent reports of clinical symptoms, age, self-reported compliance with the saliva sampling protocol, time of awakening, smoking, food consumption, exercise, or oral contraceptives (Ellenbogen et al., 2010). Furthermore, we have recently shown that high cortisol levels were predictive of the development of affective disorders one to six years later, even after

controlling for mental disorders at time 1 and parental BD (Ellenbogen et al., 2011). HPA axis functioning in individuals with BD and their offspring appears to be compromised, similarly to what has been reported in depression. However, more research is needed to understand how elevations in cortisol could lead to an increased risk for psychopathology.

3.3.2 Development and consequences of HPA abnormalities in high-risk samples

Although there is still no consensus as to whether HPA dysfunctions precede the affective disorders or represent a consequence of previous episodes, researchers have turned their attention to the possible mechanisms involved in the development of HPA abnormalities. Dysfunctions of the HPA axis may be genetically transmitted, particularly with respect to the cortisol increase following awakening (Bartels, de Geus, Kirschbaum, Sluyter, & Boomsma, 2003; Kupper et al., 2005; Wüst et al., 2004) and glucocorticoid receptor function (de Kloet & Derijk, 2004; van West et al., 2006). However, genetic liabilities in the HPA system are likely activated during the course of development by environmental events, particularly those involving parent-child interactions (Ellenbogen & Hodgins, 2009; Seckl & Meaney, 2004) and by normative developmental changes (Walker, Sabuwalla, & Huot, 2004). High cortisol levels may also be elicited by exposure to chronic and/or episodic stress at different stages of the lifetime. For instance, exposure to diverse maternal risk factors and stressful experiences occurring prenatally (O'Connor et al., 2005) and during childhood (Ellenbogen & Hodgins, 2009; Essex, Klein, Cho, & Kalin, 2002; Halligan et al., 2004; Luecken & Appelhans, 2006; Lupien, King, Meaney, & McEwen, 2000; Nicolson, 2004; van der Vegt, van der Ende, Kirschbaum, Verhulst, & Tiemeier, 2009) have been linked to increased HPA output at a

later developmental stage. Thus, it is likely that changes in cortisol levels associated with affective symptoms are elicited through a number of biopsychosocial mechanisms.

Repetti and colleagues have provided a model that could explain the link between early familial environment and HPA dysfunction in at-risk offspring (Repetti, Taylor, & Seeman, 2002; Taylor, Lerner, Sage, Lehman, & Seeman, 2004). The model describes how "risky families", characterized by neglectful parenting or conflicts within the family, can have profound effects on infants' developing emotional processing, social skills, and biological stress systems. During childhood, at-risk children fail to learn appropriate self-regulatory skills; the lack of socio-emotional skills affects coping strategies in response to stress, and this leads to chronic or recurrent activations of the stress systems. During adolescence and adulthood, interpersonal difficulties, coupled with a dysregulated HPA axis, act as risk factors for the development of mental and physical health problems. Based on this model and research in high-risk offspring, the present thesis focused on the putative interaction between exposure to interpersonal stress and cortisol at awakening and during the day in high- and low-risk offspring. Importantly, a key focus of the study was the possibility that high-risk offspring develop an enhanced sensitivity to environmental stress, possibly through a genetic susceptibility and/or early environmental exposure to high levels of stress.

4. SENSITIVITY TO STRESS AMONG THE OFFSPRING OF PARENTS WITH BIPOLAR DISORDER: A STUDY OF DAYTIME CORTISOL LEVELS

4.1 Introduction

The impact of stress on mental health varies tremendously from one person to the next. The prevailing view is that persons who are at high risk for psychopathology are more sensitive to stress, which is attributed to genetic (Gotlib et al., 2008; Kendler, Kuhn, Vittum, Prescott, & Riley, 2005), cognitive (Hankin, 2008), and family-environmental risk factors (Ellenbogen & Hodgins, 2009), or the interplay among them. Although stress reactivity to laboratory challenges has been studied in populations at risk for affective disorders (Ellenbogen et al., 2006; Gotlib et al., 2008; Hankin, Badanes, Abela, & Watamura, 2010), researchers have rarely examined the functioning of stress-sensitive biological systems in response to stress in the natural environment. The present study addresses this issue by examining the relationship between objective measures of stress in the natural environment and diurnal functioning of the hypothalamic-pituitary-adrenal (HPA) axis among the offspring of parents with bipolar disorder (OBD) and offspring of parents without a family history of affective disorders (OFH-).

The relationship between stress and affective disorders is well documented (Hammen, 2005; Kessler, 1997). Stress is typically considered to be an environmental risk factor that triggers the onset of affective episodes. However, genetic factors are known to influence a person's exposure to stressful circumstances, and the genetic liability to depression overlaps with the liability to experience stressful life events (Farmer et al., 2002; Kendler et al., 1999; Kendler & Karkowski-Shuman, 1997). These findings suggest that persons at high risk for an

affective disorder may create or engage in risky psychosocial environments, or that they may be more sensitive to negative environmental challenges. The literature to date has focused mainly on acute or episodic stress (i.e., negative life events) and its association with the onset, maintenance, and recurrence of depression (e.g., Hammen, 1991b; Mazure, 1998). Studies examining how chronic stress, defined as ongoing difficulties in multiple domains of daily roles, relates to the affective disorders are less common, and rarely have both chronic and episodic stress been assessed concurrently (Hammen et al., 2009; McGonagle & Kessler, 1990). Recently, in a sample of 816 women, the onset of a depressive episode was associated with both chronic and episodic stress, with evidence that the relationship between episodic stress and depression was more robust in participants reporting high levels of chronic stress than among those reporting low levels of chronic stress (Hammen et al., 2009). A comprehensive investigation of stress should therefore include a simultaneous examination of both episodic and chronic stress.

Changes in the HPA axis represent one possible avenue by which stress may increase the risk of developing an affective disorder (McEwen, 2008). The HPA axis orchestrates the response to prolonged challenge and facilitates recovery and adaptation to environmental change via the actions of glucocorticoids (cortisol in humans) in the periphery and central nervous system. In addition to its catabolic functions that replenish energy reserves during sustained challenge, glucocorticoids serve to suppress primary stress reactions (i.e., inflammatory and immune responses) and elicit changes in gene expression that prepare the organism for future challenges (de Kloet et al., 2008; Sapolsky et al., 2000). In persons with major depression and BD, the functioning of the HPA axis is compromised, as indicated, for example, by the overproduction and release of corticotropin releasing hormone (CRH) from

the hypothalamus, hypercortisolemia in approximately half of all patients, and disrupted negative feedback control of the axis (Gallagher, Watson, Smith, Young, & Ferrier, 2007; Meyer, Chrousos, & Gold, 2001; Schmider et al., 1995). With some exceptions (Ashman et al., 2002; Ising et al., 2005), there is increasing evidence that subtle HPA abnormalities exist prior to the onset of an affective disorder, and may represent a marker of vulnerability for these disorders (Ellenbogen et al., 2011; Ellenbogen et al., 2006; Goodyer, Herbert, Tamplin, & Altham, 2000; Lundy et al., 1999; Mannie et al., 2007; Modell et al., 1998).

The OBD are at high risk for affective disorders and other mental disorders (Birmaher et al., 2009); a review of the literature showed that the OBD are two and a half times more likely to be diagnosed with any mental disorder and four times more likely to be diagnosed with an affective disorder than offspring of parents with no mental disorder (Lapalme et al., 1997). We recently reported that the OBD experienced more chronic stress and more severe interpersonal episodic stress than the OFH-, even after controlling for affective disorders among the offspring (Ostiguy et al., 2009). We have also reported that the OBD displayed higher daytime cortisol levels in the natural environment when they were, on average, 16.7 years (Ellenbogen et al., 2006) and 18 years old (Ellenbogen et al., 2010). The latter study sampled cortisol in the afternoon over 14 days. The higher cortisol levels among the OBD as compared to the OFH- were not related to the small number of participants with diagnoses of mental disorders, nor were they associated with self-reports or parent reports of clinical symptoms, age, self-reported compliance with the saliva sampling protocol, time of awakening, smoking, food consumption, exercise, or oral contraceptives. In summary, the OBD have shown higher levels of chronic and episodic stress as well as increased daytime cortisol levels as compared to the OFH-.

Based on the stress literature and our previous findings, we hypothesized that the high daytime cortisol levels exhibited by the OBD result from an increased sensitivity to interpersonal stress. Interpersonal stress represents an important proximal risk factor for affective disorders (Eberhart & Hammen, 2006; Hammen, 2003b; Hammen et al., 2003), and has also been shown to influence HPA activity (Seeman & McEwen, 1996; Stetler & Miller, 2008). For instance, in a recent study of young women at high risk for depression, the combination of interpersonal chronic and episodic stress, but neither type of stress alone, was associated with elevated cortisol levels in the natural environment (Marin et al., 2007). To test our hypothesis, we examined whether interpersonal chronic and episodic stress moderated the relationship between elevated cortisol levels and vulnerability for an affective disorder, indexed by having a parent with BD. In all analyses, we controlled for lifetime affective disorders as well as current non-affective disorders in the offspring, controlling for disorders which have been shown to be associated with HPA dysregulation (e.g., Pajer, Gardner, Rubin, Perel, & Neal, 2001, Bhagwagar et al., 2005). Secondary analyses were conducted with non-interpersonal chronic and episodic stress, to test whether the results are specific to interpersonal stress.

4.2 Method

Sample

In the first phase of our longitudinal study, parents with a diagnosis of BD, their spouses, and children were recruited from psychiatric departments and support groups in Québec, Canada. Comparison group parents were recruited from the same neighborhoods as the parents with

BD. All parents underwent the Structured Clinical Interview (SCID-I; Spitzer et al., 1992) for *DSM-III-R* by an experienced clinician. The comparison group parents had no current or lifetime axis I disorder except for two parents diagnosed with a past episode of substance abuse, one with a past anxiety disorder, and one with both a past anxiety disorder and past substance abuse (for more information on the sample, see Ellenbogen and Hodgins, 2004).

Approximately ten years later, 123 offspring participated in a clinical re-assessment, cortisol sampling, and an information processing protocol. Of the initial sample, 18% of the OBD and 17% of the OFH- refused to participate or were not located as of January 2010. The participants and non-participants did not differ on a number of parent-rated measures, completed when the offspring were between 4 and 12 years old. The data from one participant was considered to be a statistical outlier due to extreme elevations of cortisol (over three standard deviations from the mean), and was dropped from the analyses.

The final sample included 62 OBD and 60 OFH- (64 males and 58 females), between 14 and 28 years (M = 19.48; SD = 3.38; see Table 1). The OBD were significantly older than the OFH- participants [$F(1, 120) = 7.28$, $p < 0.01$], and therefore age was included as a covariate in all analyses. Forty-two (67.7%) OBD and 26 (43.3%) OFH- were diagnosed with at least one lifetime mental disorder (see Table 2 for a list of diagnoses), and 8 OBD and 4 OFH- participants were taking medication: venlafaxine (1 OBD; 1 control), clonazepam (1 OBD), risperidone (1 OBD), divalproex (1 OBD), lithium (1 OBD), valproate semisodium (1 OBD), levothyroxine (1 OBD), dextroamphetamine (1 OFH-), omeprazole (1 OFH-), isotretinoin (1 OFH-), an unspecified decongestant (1 OBD), and an unspecified antibiotic (1 OBD).

Measures

UCLA Life Stress Interview. The UCLA Life Stress Interview (Hammen, 1991b) consists of two sections: a chronic and episodic stress assessment. The chronic stress interview assesses stress in nine domains during the last six months. Stress in each domain is coded by the interviewer on a five-point scale using specific behavioral anchor points, where 1 represents exceptionally good circumstances, and 5 indicates extremely stressful and maladaptive circumstances. Interpersonal chronic stress was defined as the sum of scores in the domains of close friends, social life, romantic, and family relationships. Non-interpersonal chronic stress was defined as the sum of scores in the domains of work, education, finances, health, and health of family members. Independent interviewers' ratings of videotaped sessions from 20 participants revealed high reliability for all domains, with a mean intraclass correlation coefficients of 0.85.

The episodic stress interview assesses stressful life events that have occurred within the last 12 months. Life events and contextual information were subsequently presented to a panel of raters blind to the risk status and mental health of the participant. The panel coded the severity of each event using a 5-point scale, and categorized them as interpersonal or non-interpersonal. Events were considered interpersonal if they resulted in a significant change in a relationship. Separate scores were computed for interpersonal and non-interpersonal events by summing the severity ratings. The interview has excellent reliability and has been used extensively in different adult and adolescent populations (Adrian & Hammen, 1993; Kim et al., 2007). Interviews were conducted by clinical psychologists who underwent extensive training and were blind to group status.

Mental Disorders. Offspring aged 19 years or older (n = 69) were interviewed with the SCID-I (First et al., 2001), and those 18 years old or younger (n = 53) with the Kiddie-Schedule for Affective Disorders and Schizophrenia- Present and Lifetime version (K-SADS-PL; Kaufman et al., 1997). The SCID-I and K-SADS-PL were administered by an experienced licensed clinical psychologist.

Cortisol sampling. Participants collected saliva at awakening, 30 and 60 minutes later, at 1300 h, 1500 h, 2000 h, and at bedtime on three consecutive days while following their usual routine. Participants were instructed to remove lipstick, to refrain from drinking water at least five minutes before sampling, and to refrain from eating, drinking (except water), smoking, and brushing teeth at least 60 min before sampling. Participants also recorded their activities prior to sampling. Saliva was expressed directly into polypropylene 6 ml vials. The vials for saliva collection were kept in larger bottles with time-stamping micro-circuitry in the cap (MEMS 6 TrackCap, Aardex Ltd, Switzerland), which automatically registered the exact time when the container was opened and closed.

Saliva samples were frozen at -20°C until assayed for cortisol by a sensitive radioimmunoassay using a commercial kits from *Diagnostic Systems Laboratory* (DSL-2000; Sanofi Diagnostics, Montréal, CAN; n = 37 (30%); 20 OBD/17 OFH-) and *MP Biomedicals* (Solon, Ohio, USA; n = 85 (70%); 42 OBD/43 OFH-). DSL abruptly stopped producing radioimmunoassay kits for cortisol during the course of the study, forcing us to switch to the use of cortisol kits from MP. We compared absolute cortisol values obtained with both kits and found that the main effect of assay kit on daytime cortisol approached significance (DSL mean cortisol = 0.602 μg/dl and MP mean cortisol = 0.499 μg/dl; p = 0.064). We controlled for assay kit by standardizing cortisol data for each kit, so that cortisol levels for both kits

had a mean of zero and a standard deviation of one (z-scores). Characteristics of the assays were similar between the two kits with a sensitivity set at 0.01 μg/dl (or 0.276 nmol/L). The inter- and intra-assay coefficients of variations for all assays were 3.4% and 4.6% for the DSL kit (on a range of 0.01-10 μg/dl dose) respectively, and 4.0% and 4.6% for the MP kit (on a range of 0.01-10 μg/dl dose) respectively.

Procedure

Written informed consent was obtained from offspring 18 years of age or older, or from parents of offspring 17 years of age or younger. At the laboratory, offspring completed the diagnostic assessment, the UCLA Life Stress Interview, and were trained to collect saliva at home as described above. Upon completion of the saliva sampling, the participants returned to the laboratory to complete questionnaires and a series of information processing tasks (not reported here). Participants were compensated $150 (CAN) for their time and related expenses.

Statistical analyses

Cortisol levels were computed as the mean of samples collected at the same time on three different days. The cortisol response following awakening was examined using area under the curve "with respect to increase" (AUC_i), a reactivity measure sensitive to changes over time (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003) and described as the most appropriate construct to examine in relation to psychosocial factors (Chida & Steptoe, 2009).

Data were also aggregated to create a measure of mean daytime cortisol level (+60 minutes after awakening, 1300 h, 1500 h, 2000 h, and bedtime samples). Aggregated and AUC_i cortisol values were standardized (see *cortisol sampling* above). No transformation of standardized cortisol values was necessary because the scores were normally distributed. Scores for chronic stress were positively skewed and therefore were log-10-transformed.

Hierarchical multiple regressions were performed on the AUC_i cortisol awakening response and mean daytime levels of cortisol. Since medications were not associated with cortisol in preliminary analyses, they were not included as a covariate in the main analyses. In all regressions, independent variables were entered in the following steps: (1) offspring age, gender, presence of a lifetime affective disorder, and presence of a current non-affective disorder; (2) interpersonal chronic stress, severity of interpersonal episodic stress, and group (risk status); and (3) interaction terms (Group × Interpersonal Chronic Stress and Group × Interpersonal Episodic Stress). Significant interactions were followed up by simple slope analyses, according to Aiken and West's guidelines (Aiken & West, 1991).

4.3 Results

Compliance

Objective examination of compliance with the saliva sampling protocol (n = 94-105) using MEMS caps indicated that, on average, the OBD and OFH- sampled, respectively, 0.8 ± 5.9 and 0.9 ± 5.4 minutes following the awakening + 30 minutes, 1.7 ± 6.1 and 2.5 ± 9.1 minutes following the awakening + 60 minutes, 11.9 ± 25.1 and 11.8 ± 22.4 minutes following 1300 h, 25.4 ± 27.4 and 24.0 ± 30.3 minutes following 1500 h, and 16.0 ± 35.0 and 20.1 ± 38.4

following 2000 h. No group differences in sampling times were detected, indicating satisfactory compliance with the saliva sampling protocol in both groups.

Interpersonal stress and the cortisol response following awakening

The regression model examining predictors of cortisol AUC_i following awakening as the dependent variable was significant ($R = 0.46$, $F(7, 112) = 3.41$, $p < 0.001$), accounting for 21.5% (R^2; adjusted $R^2 = 0.15$) of the variance. Four variables predicted cortisol AUC_i following awakening: offspring lifetime affective disorder ($\beta = 0.20$; $t = 2.22$, $p < 0.05$); female gender ($\beta = 0.23$; $t = 2.66$, $p < 0.01$); interpersonal chronic stress ($\beta = 0.42$; $t = 3.46$, $p < 0.001$); and the interaction between interpersonal chronic stress and group ($\beta = -0.32$; $t = -2.77$, $p < 0.01$). The interaction term, illustrated in Figure 1, was further examined using simple slope analyses. Results revealed that OBD who reported high levels of interpersonal chronic stress (+ 1 standard deviation [*SD*] above the mean) exhibited higher cortisol AUC_i following awakening compared to OBD who reported low levels of chronic stress (-1 *SD* below mean; simple slope $b = 4.45$, $t = 3.48$, $p < 0.001$). Among OFH- participants, the slope of the AUCi across levels of interpersonal chronic stress did not differ from zero. Thus, the OBD who experienced interpersonal chronic stress had a larger cortisol response following awakening than the OBD reporting low interpersonal chronic stress; this relationship was absent in the OFH- participants.

Interpersonal stress and daytime cortisol levels

The regression equation examining predictors of daytime cortisol levels was significant (R = 0.42, $F(9, 111) = 2.65$, $p < 0.01$), accounting for 18% (R^2; adjusted $R^2 = 0.11$) of the variance. Significant predictors of daytime cortisol levels were group (β = -0.26; t = -2.65, p < 0.01), female gender (β = 0.22; t = 2.42, $p < 0.05$), and the interaction between group and severity of interpersonal episodic stress (β = -0.31; t = -2.66, $p < 0.05$). The significant effect of group indicated that daytime cortisol levels were higher in OBD than OFH-. The interaction term, illustrated in Figure 2, was further examined using simple slope analyses. Results revealed that OBD who reported severe interpersonal episodic stress (+ 1 *SD* above the mean) exhibited higher levels of daytime cortisol compared to OBD reporting lower levels of interpersonal episodic stress (simple slope, $b = 0.17$, t = 1,74, $p = 0.08$), although the finding fell short of conventional statistical significance. Among OFH- participants, the slope of daytime cortisol across levels of interpersonal episodic stress did not differ from zero. Thus, the OBD who reported severe interpersonal episodic stress exhibited higher levels of daytime cortisol than the OBD reporting mild interpersonal episodic stress; this relationship was absent in the OFH- participants.

Secondary analyses: Non-interpersonal stress and cortisol levels

Two additional hierarchical multiple regressions were conducted to examine whether indices of non-interpersonal stress also predicted cortisol AUC_i following awakening and daytime cortisol levels. The interaction between non-interpersonal chronic stress and group (β= -0.26;

t = -2.31, $p < 0.05$) predicted AUC_i following awakening. Consistent with interpersonal stress findings, simple slope analyses of the interaction term revealed that the OBD who reported high levels of non-interpersonal chronic stress exhibited high cortisol AUC_i following awakening compared to the OBD reporting low levels of non-interpersonal chronic stress, although the finding did not reach conventional statistical significance (simple slope, b = 2.15, t = 1.55, p = 0.12). In the OFH-, the slope did not differ from zero. Daytime cortisol levels were not associated with either chronic or episodic non-interpersonal stress.

4.4 Discussion

The present study sought to determine if interpersonal chronic and episodic stress moderated the relationship between risk status, defined as having a parent with BD, and cortisol levels measured seven times over three consecutive days in the natural environment. Four key findings emerged. First, the OBD exhibited higher levels of daytime cortisol than the OFH-, replicating our previous findings in this sample when the OBD were, on average, aged 16.7 and 18 years (Ellenbogen et al., 2006; 2010). Second, ratings of chronic stress, collapsed across group, predicted the cortisol response following awakening. Third, the OBD experiencing high levels of interpersonal chronic stress exhibited higher HPA axis reactivity following awakening than the OBD who reported low levels of interpersonal chronic stress. By contrast, among the OFH-, no associations were detected between chronic stress and cortisol levels following awakening. Unexpectedly, the interaction between non-interpersonal chronic stress and group also predicted the cortisol awakening response. Finally, the OBD experiencing severe interpersonal episodic stress had higher cortisol levels during the day

than the OBD experiencing mild interpersonal episodic stress. Again, among the OFH-, no associations were detected between daytime cortisol levels and episodic stress, and no significant findings in either group were observed for non-interpersonal episodic stress. Importantly, each of the observed interactions between group, defined by family history, and stress that predicted cortisol levels were significant after controlling for offspring age, gender, lifetime affective disorders, and current non-affective disorders.

The observed interactions between stress and group suggest that the OBD are physiologically more sensitive to stress in the natural environment than OFH- participants. An increased sensitivity to stress, particularly in interpersonal domains, may partly explain our consistent findings of higher daytime cortisol levels among the OBD than OFH- during adolescence and young adulthood (Ellenbogen et al., 2006; 2010), as well as a similar finding in the offspring of parents with major depression (Mannie et al., 2007). Interestingly, two studies of the OBD have failed to find evidence of an increased sensitivity to stressful life events when examining the relationship between family history of affective disorders and the onset of an affective disorder (Hillegers et al., 2004; Wals et al., 2005). Because these studies did not include a control sample, they are not comparable to the present study. Moreover, the difference between studies may indicate that increased stress sensitivity in the OBD is specific to the functioning of the HPA axis. The results of the present study, however, are consistent with those from other longitudinal investigations that have highlighted the role of stress and stress sensitivity in the development of affective disorders (Caspi et al., 2003; Espejo et al., 2006; Kendler et al., 2005; Wichers et al., 2009). A recent study of 502 female twins showed that stress sensitivity (conceptualized as negative affect following daily stress) was predictive of future depressive symptoms as well as major depressive disorder (Wichers

et al., 2009). A study of the offspring of parents with major depression demonstrated that girls who were homozygous for the short allele in the promoter region of the serotonin transporter (5-HTTLPR) gene exhibited increased HPA axis reactivity to a laboratory stressor compared to girls with a least one long allele (Gotlib et al., 2008). Similarly, among a sample of 393 adolescents at risk for psychopathology, high morning cortisol levels sampled in the natural environment were associated with carrier status of short allele of the 5-HTTLPR gene (Goodyer et al., 2009). Interestingly, the relationship between elevated cortisol levels and the subsequent development of depression was moderated by the 5-HTTLPR gene polymorphism. Thus, an increased sensitivity to stress may represent an important risk factor for the development of an affective disorder and the sensitivity to stress may be genetically determined.

The sensitivity to stress displayed by the OBD may also result, at least in part, from a long history of stressful experiences. The OBD were raised in chaotic family environments, in which parents provided low levels of structure and modelled ineffective skills for coping with stress (Chang et al., 2001; Ellenbogen & Hodgins, 2009; Ostiguy, Ellenbogen, & Hodgins, in press). It is well established that exposure to a stressful environment in early life, as indexed by maternal anxiety and depression (Halligan et al., 2004; O'Connor et al., 2005), poverty (Lupien et al., 2000), or non-optimal parenting practices (Ellenbogen & Hodgins, 2009; Ostiguy et al., in press), affects the development and sensitivity of the HPA axis and the methylation of genes that regulate HPA functioning (Heim, Owens, Plotsky, & Nemeroff, 1997; Weaver et al., 2004). Environmental factors may also alter other putative risk factors, such as cognitive vulnerability and changes in appraisal (Alloy, Abramson, Walshaw, Keyser, & Gerstein, 2006), which could subsequently increase the HPA response in the

natural environment. Thus, an early stressful family environment, genes, or a combination of both may sensitize the HPA axis to stress through different mechanisms. Genetically-informed longitudinal investigations are needed to further elucidate the determinants of increased sensitivity to stress.

The present study observed that chronic stress predicted the cortisol response following awakening but not daytime cortisol levels, and that episodic stress predicted cortisol levels in the daytime but not the awakening response. These findings are consistent with evidence that cortisol levels following awakening and in the afternoon are regulated by different psychobiological factors (Clow et al., 2004). The cortisol rise following awakening is partly determined by genetic factors (Wüst et al., 2004), by distal factors such as stressful experiences in childhood (Meinlschmidt & Heim, 2005), longstanding medical conditions, and chronic stress (Pruessner, Hellhammer, & Kirschbaum, 1999; Therrien et al., 2008). By contrast, evidence suggests that cortisol levels during the rest of the day are determined primarily by shared (Schreiber et al., 2006) and non-shared environmental factors (Kupper et al., 2005), consistent with the association between interpersonal episodic stress and elevated daytime cortisol levels. Further, the increase in cortisol levels following awakening and cortisol levels measured at other times are not correlated (Edwards et al., 2001), supporting the premise that the rise in cortisol following awakening is regulated by a different mechanism than that controlling cortisol levels during the rest of the diurnal cycle (Clow et al., 2004).

Limitations of the study warrant consideration. The participants varied in age from 14 to 28 years, but the younger (age 14 to 18) and older (age 19 to 28) participants did not differ significantly on any of the stress scores. Although many confounding influences on salivary

cortisol levels were assessed in this study, menstrual cycle phase was not measured. Despite having objective measures of sampling compliance (i.e., vial lids with time-stamping microcircuitry), the exact time of awakening was not objectively verified leaving open the possibility that some samples were collected sometime after awakening. There were no group differences in sampling compliance, suggesting that delays in taking the saliva sample after awakening had no influence on the findings. As a precaution, however, future studies should adopt ambulatory monitors of physical activity in order to objectively measure the time of awakening. The present results derive from the study of an ethnically homogeneous sample of OBD and OFH- from the province of Québec (Canada). It is not known whether the findings will generalize to other populations of high-risk offspring. Moreover, this study is cross-sectional, and thus, the direction of the associations between stress and cortisol levels cannot be determined. Finally, the interpersonal episodic stressors were not overlapping in time with the measurement of cortisol. Therefore we cannot conclude that the episodic stress led directly to the elevation in cortisol. Future studies in high-risk populations could benefit from the use of time-linked ambulatory protocols assessing episodic stress and cortisol levels concurrently.

In conclusion, the OBD exposed to high levels of stress in their natural environment exhibited higher cortisol levels than the OBD exposed to lower levels of stress. The observed associations were absent among offspring with no family history of affective disorders, suggesting that the OBD have a biological sensitivity to stress, particularly with respect to interpersonal difficulties. This finding has direct implications for the development of affective disorders, as high cortisol levels in vulnerable populations are associated with an increased risk of developing an affective disorder (Ellenbogen et al., 2011; Goodyer et al.,

2009). Importantly, the high cortisol levels exhibited by the OBD (Ellenbogen et al., 2006; 2010) were attenuated in those reporting low levels of stress, suggesting that the vulnerability associated with a family history of affective disorders may be mitigated by environmental interventions.

Table 1: Descriptive and demographic information for the OBD and the OFH-.

	OBD		**OFH-**		***F***[a]
N	62		60		*ns*
Gender (Male:Female)	36:26		28:32		-
Mean age (years) ± *SD*	20.27 ± 3.37		18.67 ± 3.20		7.28**
Mean interpersonal chronic stress ± *SD*	2.17 ± 0.52		1.86 ± 0.37		13.72***
Mean non-interpersonal chronic stress ± *SD*	2.34 ± 0.51		1.99 ± 0.32		19.65***
Mean severity of interpersonal episodic stress ± *SD*	1.19 ± 1.27		1.32 ± 1.42		*ns*
Mean severity of non-interpersonal episodic stress ± *SD*	1.37 ± 1.43		1.14 ± 1.32		*ns*
Cortisol concentration	**Raw (μg/dl)**	**z-score**	**Raw (μg/dl)**	**z-score**	
AUC with respect to increase at awakening ± *SD*	0.09 ± 0.16	-0.02 ± 1.02	0.09 ± 0.15	0.01 ± 0.92	*ns*
Mean daytime cortisol concentration ± *SD*	0.60 ± 0.29	0.23 ± 0.99	0.46 ± 0.26	-0.23 ± 0.95	6.86**
Mean awakening cortisol ± *SD*	0.19 ± 0.09	0.19 ± 1.00	0.15 ± 0.08	-0.22 ± 0.94	5.24*
Mean +30 minutes cortisol ± *SD*	0.27 ± 0.16	0.15 ± 1.03	0.22 ± 0.13	-0.15 ± 0.95	*ns*
Mean +60 minutes cortisol ± *SD*	0.22 ± 0.11	0.13 ± 0.85	0.19 ± 0.15	-0.14 ± 1.12	*ns*
Mean 13:00 h cortisol ± *SD*	0.13 ± 0.10	0.22 ± 1.14	0.10 ± 0.06	-0.23 ± 0.76	6.76 *
Mean 15:00 h cortisol ± *SD*	0.10 ± 0.07	0.22 ± 1.13	0.08 ± 0.04	-0.24 ± 0.77	6.96**
Mean 20:00 h cortisol ± *SD*	0.08 ± 0.06	0.23 ± 1.10	0.06 ± 0.04	-0.23 ± 0.82	6.82**
Mean bedtime cortisol ± *SD*	0.06 ± 0.05	0.15 ± 1.07	0.04 ± 0.04	-0.16 ± 0.90	*ns*

Notes. OBD = Offspring of a parent with bipolar disorder; OFH- = Offspring with no family history of affective disorders; *SD* = Standard Deviation.

[a] F statistics based on two-tailed one-way ANOVAs of the standardized data (z-scores).

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

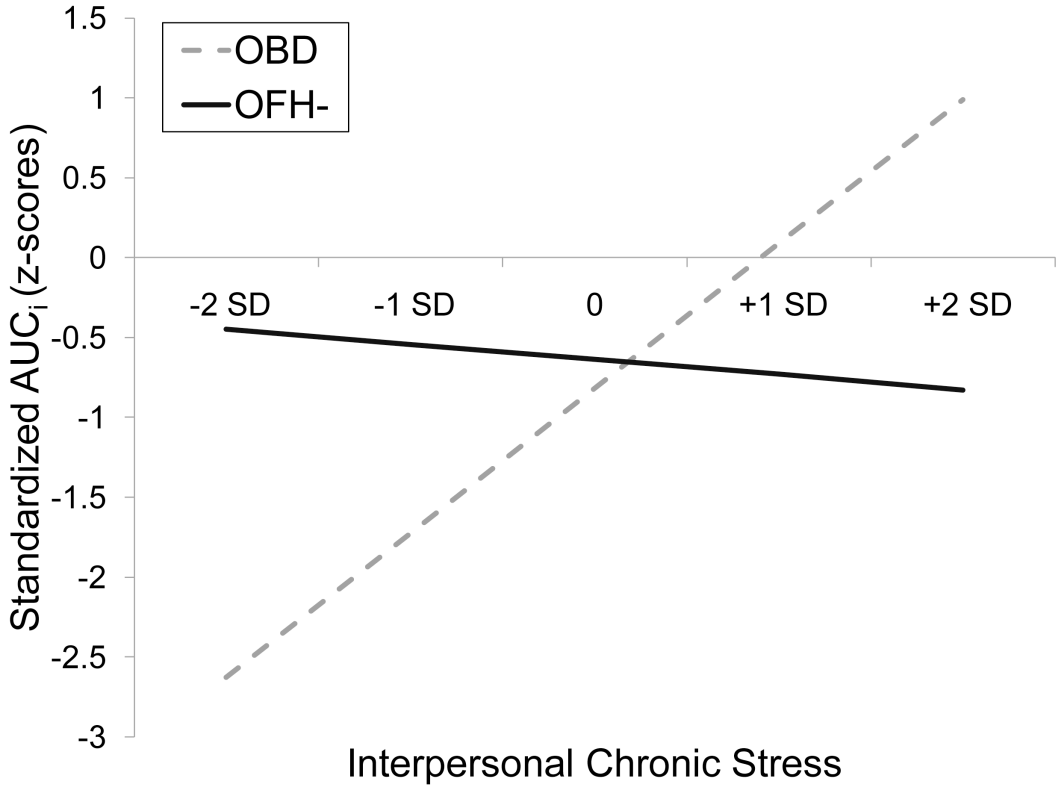
Table 2: Psychiatric diagnoses for the OBD and the OFH-.

Diagnoses	OBD		OFH-	
	Current	Past	Current	Past
Affective disorders	5	15	0	6
Major depressive disorder	1	15	0	6
Bipolar disorder I	2	0	0	0
Bipolar disorder II	2	0	0	0
Anxiety disorders	21	6	10	1
Social phobia	4	1	3	0
Specific phobia	8	1	5	1
Generalized anxiety disorder	6	0	2	0
Post-traumatic stress disorder	0	3	0	0
Obsessive-compulsive disorder	0	1	0	0
Panic disorder/agoraphobia	3	0	0	0
Externalizing disorders	14	14	6	9
Alcohol abuse/dependence	2	2	3	0
Drug abuse/dependence	10	11	2	7
Attention deficit/hyperactivity disorder	2	0	1	0
Conduct disorder/oppositional defiant disorder	0	1	0	2
Other diagnoses [a]	1	5	1	6
Total	41	40	17	22

Notes. OBD = Offspring of a parent with bipolar disorder; OFH- = Offspring with no family history of affective disorders

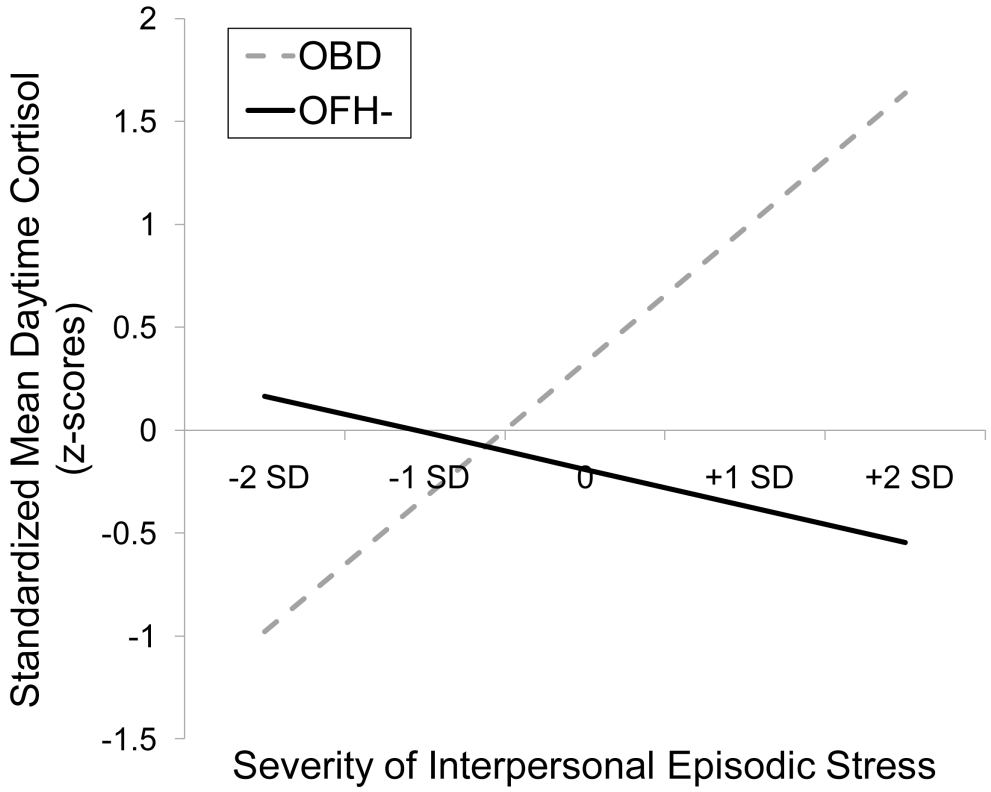
[a] Other diagnoses include past adjustment disorder with depressive symptoms (n = 3); past separation anxiety (n = 1), past enuresis (n = 4), past motor/vocal tic (n = 2), hypochondriasis (n = 1), current anorexia nervosa (n = 1), and past PCP-induced psychotic disorder (n = 1).

Figure 1: Interaction between group and interpersonal chronic stress predicting area under the curve with respect to increase.



Depiction of the significant interaction between group and interpersonal chronic stress predicting the area under the curve with respect to increase (AUC_i) for the cortisol response following awakening. The offspring of parents with bipolar disorder (OBD) who reported high levels of interpersonal chronic stress [1 or more standard deviations (*SD*s) above the mean] had greater HPA axis reactivity following awakening than the OBD who reported low levels of interpersonal chronic stress. No relationship between stress and HPA axis reactivity was observed among the offspring of parents with no history of affective disorders (OFH-).

Figure 2: Interaction between group and the severity of interpersonal episodic stress predicting mean daytime cortisol.



Depiction of the significant interaction between group and the severity of interpersonal episodic stress predicting mean daytime cortisol. The offspring of parents with bipolar disorder (OBD) who reported more severe negative life events [1 or more standard deviations (*SD*s) above the mean] had higher mean daytime cortisol levels than the OBD who reported less severe negative life events. No relationship between stress and daytime cortisol levels was observed among the offspring of parents with no history of affective disorders (OFH-).

5. GENERAL DISCUSSION

The studies included in this dissertation add to the small body of research devoted to understanding developmental trajectories and vulnerability among the OBD, who are at high risk for developing an affective disorder and other negative outcomes. The first manuscript shed light on a developmental pathway from parents' personality to offspring's negative outcomes in childhood and early adulthood, while controlling for offspring age, gender, and presence of any current disorder. More precisely, our longitudinal study showed that parents' neuroticism and agreeableness predicted internalizing and externalizing behaviours during childhood. In turn, childhood problem behaviours predicted poor interpersonal functioning with family members, peers and romantic partners 10 years later. Since these associations were found in the entire sample of OBD and control offspring, we then examined the moderating effect of parents' BD diagnosis. A diagnosis of BD in the parents moderated the association between parents' neuroticism and childhood internalizing problems, but not the association between childhood internalizing problems and interpersonal functioning among the offspring a decade later. These findings are particularly interesting because internalizing problems appear to represent an important early marker of risk among families where parents have BD and high neuroticism, but once childhood internalizing problems have developed, they are likely to lead to chronic interpersonal stress, regardless of risk status.

While the first manuscript highlighted the developmental antecedents of poor interpersonal functioning, the second manuscript examined a putative consequence of poor interpersonal functioning and exposure to SLEs. Chronic interpersonal and non-interpersonal problems moderated the relationship between the cortisol response following awakening and

risk status; interpersonal SLEs moderated the relationship between mean daytime cortisol levels and risk status. In both moderation models, the OBD experiencing high levels of interpersonal stress exhibited higher cortisol levels compared to the OBD who reported low levels of stress. In contrast, among the controls, no associations were detected between stress and cortisol levels. These results suggest that, during adolescence and early adulthood, the OBD show evidence of a biological sensitivity to interpersonal stress that is not evident in the control group. It should be noted, however, that the findings for the cortisol response following awakening was associated to chronic stress in general, whether it was interpersonal or non-interpersonal in nature. For mean daytime cortisol levels, the relationship was specific to interpersonal SLEs.

The impact of stress on mental health varies tremendously from one person to the next, suggesting that some people are more sensitive and others are more resilient to the effects of stress. The prevailing view is that persons who are at high risk for psychopathology are more sensitive to stress, which is attributed to genetic (Gotlib et al., 2008; Kendler et al., 2005), cognitive (Hankin, 2008), and family-environmental risk factors (Ellenbogen & Hodgins, 2009), or the interplay among them. The early stress sensitization phenomenon has been put forth to explain individual differences in stress sensitivity; this theory stems from research showing that early adverse life events can alter the stress system (Halligan et al., 2004; Lupien et al., 2000; Lupien et al., 2009; O'Connor et al., 2005), sensitizing it to future stress (Post, Leverich, Xing, & Weiss, 2001). Hammen and colleagues (2000) found support for the stress sensitization hypothesis in young women, showing that those exposed to early adversity (e.g., family violence, parent psychopathology, parental divorce, etc.) were more likely to become depressed following less SLEs than women not exposed to early adversity.

In a sample of individuals suffering from BD I, Dienes and colleagues found support for the stress sensitization theory; participants who experienced a severe stressor before 12 years old relapsed with lower levels of stress compared to participants with mild or no early adverse events (Dienes, Hammen, Henry, Cohen, & Daley, 2006). The results of the present study showed that in the OBD, but not the controls, cortisol levels were correlated with interpersonal chronic and episodic stress. These results are consistent with the early stress sensitization theory, as we can speculate that the OBD are much more likely than the control participants to have experienced early stressors, due to the chaotic nature of their parents' disorder. This increased biological sensitivity to interpersonal stress in the OBD might be an example of sensitization of the stress system that occurs following early adversity, which then increases vulnerability for the affective disorders (Ellenbogen et al., 2011).

Two studies have now shown that high cortisol levels in vulnerable populations are associated with an increased risk of developing an affective disorder (Goodyer et al., 2009; Ellenbogen et al., 2011). Indeed, we recently found that high levels of daytime cortisol, measured in the natural environment, doubled the risk of developing an affective disorder one to six years after cortisol sampling (Ellenbogen et al., 2011). This prediction remained significant after controlling for previous mental disorders in the offspring and BD diagnosis in the parents. Recent studies have shed light onto a possible biological pathway responsible for the increased risk for psychopathology in individuals with elevated cortisol levels. A polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR) has been implicated in the development of depression in response to stress (Caspi et al., 2003; Kendler et al., 2005; Wilhelm et al., 2006; for exception, see Risch et al., 2009). For example, individuals with one or two short (s) alleles of 5-HTTLPR polymorphism were

more likely to show depressive symptoms or a depressive episode as a function of SLEs compared to individuals with two long (l) alleles (Caspi et al., 2003). Gotlib and colleagues (2008) recruited adolescent girls at high and low risk for depression, genotyped them for the 5-HTTLPR polymorphism, and had them complete a laboratory stressor. Girls with the s/s polymorphism exhibited higher levels of salivary cortisol during and after the stressor compared to girls with the s/l or l/l polymorphism. Therefore, individuals possessing the s/s allele appear to be more sensitive to stress, with respect to HPA axis activity. In other words, individuals with the s/s alleles might have a lower HPA axis activation threshold in response to stress compared to s/l or l/l individuals, making them biologically at risk for the future development of affective disorders. Interestingly, high morning cortisol levels in adolescents having high-risk 5-HTTLPR polymorphism predicted depression onset 12 months later (Goodyer et al., 2009). It can be concluded that psychosocial interventions aimed at decreasing stress reactivity – and HPA reactivity – might be beneficial in reducing vulnerability to affective disorders. It remains to be seen if this biological vulnerability applies to the OBD and individuals with BD, as most of the research described above were conducted with depressed individuals. Our results provide some evidence of a sensitivity to interpersonal stress among the OBD, as evidenced by increased levels of awakening and daytime cortisol, but more research is needed in this population.

The findings described in this dissertation are also particularly interesting when added to the literature showing that poor interpersonal functioning is a vulnerability factor for affective disorders (e.g., Hammen, 2003, Hammen et al., 2001; Eberhart & Hammen, 2006). As described above, the link between SLEs and daytime cortisol was specific to stressors of an interpersonal nature. Given the immense individual and societal cost of BD and

depression (Murray & Lopez, 1997), targeted early interventions are warranted in the OBD. Theoretically, the results of the present studies highlight the need to intervene during early childhood in order to prevent the development of childhood behavioural problems and future interpersonal difficulties. Moreover, it is plausible that, based on a number of studies (e.g., O'Connor et al., 2005), early family interventions aimed at reducing adverse events and stress exposure in children could perhaps prevent the early sensitization of the HPA axis among high-risk offspring.

Although many researchers agree that prevention interventions are needed (Salvadore, Drevets, Henter, Zarate, & Manji, 2008), little research efforts have been put into the development and evaluation of such interventions in high-risk offspring. Research to date has shown that psychosocial treatment interventions can reduce symptomatology in children and adolescents suffering from BD. For instance, individual family psychoeducation and cognitive behavioural therapy are effective in reducing BD symptoms (Feeny, Danielson, Schwartz, Youngstrom, & Findling, 2006; Fristad, Gavazzi, & Mackinaw-Koons, 2003). With regard to prevention, psychoeducation for families with a depressed parent have been effective in decreasing problematic behaviours in the children (Beardslee & Gladstone, 2001) and cognitive therapy was shown to reduce the risk of psychosis in individuals at ultra-high risk for psychotic disorders (Morrison et al., 2004). At least three studies have shown that the intergenerational transmission of depression had been attenuated after psychosocial interventions (Garber et al., 2009; Swartz et al., 2008; Weissman, Pilowsky, et al., 2006). To our knowledge, only one project has been conducted to test the feasibility of prevention interventions in the OBD. Miklowitz and colleagues (2008) reviewed the literature on the OBD and identified three markers of risk for the development of BD, above and beyond a

familial history of BD. They identified children with the following characteristics to be at higher risk: 1) children showing subsyndromal forms of BD (e.g., cyclothymia), 2) children who have experienced a major depressive episode and some sub-clinical manic symptoms, and 3) children with ADHD combined with mood swings. Therefore, these high-risk offspring were already diagnosed with one disorder, but were targeted as being at particularly high risk for a transition to BD. Their treatment was based on the principles of family-focused therapy, which aims at helping family achieve a new equilibrium when faced with challenges (Miklowitz, 2008). The therapy included psychoeducation, communication enhancement training, and problem-solving skills training, aimed at improving parenting skills, teaching parents to recognize early symptoms of BD in their offspring, and developing stress management techniques in the offspring. This family-focused therapy for high-risk offspring was recently tested in an open trial in a sample of 13 children, aged 9 to 16 years (Miklowitz et al., 2011). Children and their parents attended sessions for 12 weeks and participated in a one-year follow-up. After one year, the OBD reported decreased depressive and hypomanic symptoms as well as increased global functioning. These unique data show that short-term prevention interventions are both feasible and efficacious and pave the way for future research.

Based on the findings of this dissertation, it seems that the offspring of parents with high neuroticism and BD are at particularly high risk for negative outcomes and should be a priority group for prevention interventions. Ideally, interventions should aim at identifying these ultra high-risk offspring no later than middle childhood, with a focus on reducing internalizing problems. Indeed, we have shown that once internalizing problems develop, they tend to evolve into chronic interpersonal problems, regardless of parental personality or

BD. Interpersonal problems have been shown to predict depression (e.g., Eberhart & Hammen, 2006), which often predates the development of BD in high-risk offspring (Duffy et al., 2010). Therefore, interventions aimed at diminishing internalizing symptoms could prevent the OBD from developing poor interpersonal functioning and, possibly, from developing a chronic, devastating mental illness.

Based on studies of early intervention in low socioeconomic status families, preventive interventions could also improve both child and parent physical health (e.g., Olds et al., 1998). For instance, nurse visits during and after pregnancy in a low SES neighbourhood have shown to reduce antisocial and risky behaviours in the offspring 15 years later (Olds et al., 1998). Theoretically, prevention interventions like the one described above could perhaps help reduce high cortisol levels in the OBD and their parents, possibly decreasing allostatic load and its negative effects on the HPA system. As described previously, allostatic load occurs when the HPA axis is overly activated and not properly shut down; it is associated with obesity, hypertension, cardiovascular disease and memory loss, to name a few (e.g., Lupien et al., 2009). Past research has shown that positive interactions and social support can dampen the HPA axis activity in response to stress (Ditzen et al., 2007; Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003). Furthermore, cognitive interventions in individuals with panic disorder can modulate the HPA response (Abelson, Liberzon, Young, & Khan, 2005). Therefore, in addition to the prevention of mental illness, psychosocial interventions in high-risk offspring and their parents could play a role in the prevention of chronic physical problems, which are also very costly to society.

Furthermore, family interventions could have an impact on the course of the parents' disorder. Interventions in families with a parent having BD should emphasize optimal

treatment of parental BD, as a significant portion of the offspring's stress stem from familial difficulties and improperly managed BD (Ostiguy et al., 2009). Although pharmacology and psychotherapy have been shown to be efficacious in decreasing mood swings and preventing relapse (for review, see Goodwin & Jamison 2007; Soares-Weiser et al., 2007), mortality and morbidity rates in BD patients have improved very little in the last 20 years (Angst, Angst, Gerber-Werder, & Gamma, 2005; Kasper, 2004). Consequently, prevention of such a debilitating, chronic disorder should be the main goal of research with high-risk offspring, but given that living with a parent with BD is an enormous burden and stressor, research should continue to focus on adequate treatment of BD as well. Similarly, it has been found that stress can lead to a relapse of manic or depressive episodes in individuals with BD (Cohen et al., 2004; Hammen & Gitlin, 1997). Research in the offspring of parents with depression has supported a bidirectional relationship between the offspring's difficulties and parents' mood (Elgar, Curtis, McGrath, Waschbusch, & Stewart, 2003; Forehand & McCombs, 1988). Therefore, the OBD's SLEs and interpersonal conflicts may influence the environment of these high-risk families, and, in turn, the parents' stress level and risk for relapse. A relapse in the parent could then add to the child's stress levels and further increase the risk of developing an affective disorder. It is thus likely that prevention interventions targeting the entire family could have positive effects in the offspring and important benefits in the parents, perhaps improving the course of BD. Futures studies of families with a BD parent should endeavor to understand how concurrent changes in child and parent functioning impact upon each others mental health, both in the short and long-term.

As data accumulate on prevention interventions, one wonders, who should be responsible for identifying high-risk offspring? Swann and colleagues (2005) argue that

primary care providers should be trained in detecting BD early. The authors highlight four characteristics that need to be assessed if observed in young patients (depression, irritability, mood lability and problematic impulsivity); if the health care provider suspects BD, then they should refer the patient to a psychiatrist for further evaluation. Given the high prevalence of mental health problems in offspring, primary care physicians in the care of a BD parent may want to periodically assess offspring. The Mental Health Commission of Canada's "child and youth" advisory committee generated close to 20 recommendations for the implementation of prevention interventions in at risk youth, including the involvement of primary care providers, teachers, educators, and recreational staff, in an attempt to identify as many youth in need as possible (Kutcher, McLuckie, & Child and Youth Advisory Committee, 2010).

5.1 Limitations and methodological considerations

Several methodological limitations warrant discussion. First, the difference between psychopathology and neuroticism is difficult to establish. The association between psychopathology and neuroticism is an area for theoretical discussion and there is a paucity of research on this topic. There is certainly overlap between the two concepts, and the exact nature of this association is not fully known. Many possibilities have been put forth, such as personality and psychopathology sharing a common aetiology, personality being a precursor to psychopathology, and psychopathology impacting personality (e.g., Klein et al., 2002). With regard to neuroticism and affective disorders, research points to two models: a concomitant model in which neuroticism is influenced by mood, and a precursor model, in which neuroticism influences the course of affective disorders (Klein et al., 2002).

There is a high genetic association between affective disorders and neuroticism (Hettema et al., 2006; Kendler et al., 2006). In a previous study of the OBD (Ellenbogen & Hodgins, 2004), high levels of neuroticism in the parents were associated with poor psychosocial functioning and problematic behaviours among their offspring, independently of the presence of an affective disorder in the parents. These data show that neuroticism in parents has a robust and unique contribution to the concurrent prediction of problems in children. Study 1 argues that parents' personality traits are important predictors of long-term outcomes in their offspring, above and beyond the influence of an affective disorder. We propose that personality explains some of the environmental risk effects associated with growing up in a family with a parent having an affective disorder. More efforts should be made towards understanding gene-environment correlations; that is, the hypothesis that the genetic susceptibility associated with having a parent with BD influences outcomes not only through the transmission of genes, but also through its effects on the environment (Rutter, 2007).

A second limitation, specific to the second study, is the lack of objective compliance data for the offspring's awakening time. Future studies should adopt ambulatory monitors of physical activity in order to objectively measure the time of awakening. Although we used vials with time-stamping micro-technology as an objective measure of compliance, they do not provide information regarding the actual time of awakening, only the time that the sample was taken. In order to increase compliance at awakening, participants were given very specific instructions about the importance of sampling at the appropriate time, both verbally and in writing. Participants were instructed to keep the vials on the nightstand, next to their alarm clock, to take the saliva sample before getting out of bed as soon as they

awoke, and to postpone saliva sampling to the next morning if they failed to take the first sample as soon as they awoke. We believe that compliance was higher in the morning than the afternoon because of these specific instructions. Compliance with the sampling procedure may have decreased in the afternoon because of a lack of reminders and in some instances, because participants found themselves in situations where sampling was not possible (e.g., a college classroom). The other important factor in our research is that we have been working with these families for over 10 years now. We think that our longstanding relationship with our participants, and our efforts to educate them about the importance of sampling at the appropriate time, increased their compliance. Furthermore, previous research has shown that participants who were told of the vials function were more compliant with the research protocol than participants who were not told about the recording function (Kudielka, Broderick, & Kirschbaum, 2003). Moreover, one of the advantages of collecting multiple samples across different times and different days is that error variance due to factors such as poor compliance is diminished. Thus, in accordance with Goodyer and colleagues' (2001) recommendations, our cortisol values are based on nine samples for the awakening response (three samples × three days) and 15 samples for the daytime cortisol (five samples × three days). Finally, we have found no evidence of group differences with respect to any measure of sampling compliance. Therefore, it is likely that any variance in sampling compliance would have influenced both groups in a similar fashion.

A third limitation stems from the cross-sectional design of study two. Our interpretations focused primarily on the relationship between interpersonal stress and its impact on the HPA axis in the OBD participants. However, perhaps it is possible that the OBD experienced elevated chronic and episodic stress as a result of long-term alterations in

the HPA axis. Prospective, longitudinal studies are needed to elucidate which factors are temporally associated with subsequent changes in an outcome measure.

Fourth, despite arguing for a significant impact of parental diagnosis and personality on the children's problem behaviours and functioning, we did not control for other important parental variables such as current symptomatology or SLEs. We have just completed a partial re-assessment of the parents in this study, after collecting data on the number of hospitalizations and episodes, income, employment stability, social support, chronic and episodic stress, as well as many other variables pertaining to their functioning. Future data analyses in this sample will include a number of parental variables as covariates (e.g., Bella et al., 2011); however, it was not feasible with the current projects, as we do not have data from the full sample of parents yet. The future inclusion of parents' data as control variables will enable us to better understand the impact of parents as a distinct risk factor from the offspring own stress and functioning.

Finally, despite the number of studies showing the importance of interpersonal difficulties in the development and maintenance of affective disorders, no consensus has emerged as to how to measure interpersonal functioning. Interpersonal functioning, usually measured with questionnaires, and sometimes through observation, has been equated with social competence, interpersonal problem-solving skills, relationship quality, peer acceptance, and social support. Therefore, reviewing the literature on interpersonal functioning is limited by the inconsistency in measurement tools and concept definition. Efforts should be made towards defining the key facets of interpersonal functioning, which could then be used to identify existing tools or to create new tools in order to measure the concept reliably.

5.2 Future directions and conclusions

First, prevention of affective disorders through targeted interventions relies on early recognition of high-risk offspring. Indeed, only a portion of the OBD develop BD in their lifetime (around 20-30%; Geller, Fox, & Clark, 1994); thus, it is essential to identify characteristics associated with the future development of BD, above and beyond a family history of the disorder (Chang, Howe, Gallelli, & Miklowitz, 2006; Chang, Steiner, Dienes, Adleman, & Ketter, 2003; Correll et al., 2007). For instance, the pursuit of endophenotypes, or heritable biomarkers, has gained interest. Certain brain regions – especially within the prefrontal-limbic system – have been implicated in the pathophysiology of BD (Strakowski, DelBello, Adler, Cecil, & Sax, 2000). Other candidate endophenotypes of BD are temperament (e.g., Chang et al., 2003) and REM sleep (e.g., Hasler, Drevets, Gould, Gottesman & Manji, 2006). Similarly, it might be beneficial to study the different developmental pathways leading to BD in greater detail. For instance, quite a bit of research has been done on the role of ADHD, anxiety disorders, and internalizing and externalizing problems as precursors to BD (Chang, Steiner, & Ketter, 2000; Duffy et al., 2010; Klimes-Dougan et al., 2010). These problems during childhood and adolescence may signal a trajectory to affective disorders (Duffy et al., 2010). Similarly to the first manuscript, which highlights pathways leading to problem behaviours and interpersonal dysfunction, future longitudinal studies should try to identify developmental markers of risk in order to refine the identification of OBD who are at very high risk and more likely to benefit from interventions. Perhaps future research could build on the present findings, which tentatively highlight possible "ultra" high-risk youth: the offspring of parents with high neuroticism and BD, the

OBD with internalizing symptoms, the OBD with high cortisol levels, and the OBD with interpersonal difficulties.

In line with the prevention interventions and identification of high-risk offspring, a second direction for future studies should be to investigate the safety and efficacy of mood stabilizer treatment of high-risk youth exhibiting affective symptoms. One study has used divalproex, a mood stabilizer used for BD, in affected OBD (Chang, Dienes, et al., 2003). The 24 OBD recruited for the open trial study were diagnosed with current or past depression, ADHD, dysthymia, or cyclothymia. Over a 12-week follow-up period, there was a significant decrease in manic and depressive symptoms and a general improvement in disorder severity in the sample. This line of research is particularly important, knowing that antidepressant or stimulant treatment, which could be prescribed to children diagnosed with depression or ADHD, can act as a trigger for manic symptoms in at-risk individuals (e.g., Venkataraman, Naylor, & King, 1992; Koehler-Troy, Strobber, & Malenbaum, 1986). Furthermore, Gottesman and Erlenmeyer-Kimling (2001) caution medical professionals against the indiscriminant prescription of medication to affected children and adolescent, as what looks like a prodromal condition may never progress to a full diagnosis. Thus, in order to better understand the risks and benefits of mood stabilizers in affected OBD, randomized, placebo-controlled, longitudinal trials need to be designed and implemented.

Finally, it is not known whether pre-pubertal OBD show the same elevation in cortisol that we have observed in adolescent and adult OBD (Ellenbogen et al., 2006; 2010). Studies of pre-pubertal children experiencing high familial stress (Badanes, Watamura, & Hankin, 2011) or exhibiting dysphoric mood (Hankin et al., 2010) show lower cortisol levels following laboratory stressors compared to control children. Basal cortisol levels (Puig-

Antich et al., 1989) and cortisol levels in response to the dexamethasone suppression test (Birmaher et al., 1992) were not significantly different between pre-pubertal depressed children and control children. No studies of cortisol in pre-pubertal OBD have been conducted. There is therefore a gap in our understanding of the internal (e.g., puberty) and external factors influencing HPA axis functioning. Future longitudinal studies are needed in pre-pubertal high-risk offspring to determine which developmental factors are associated with future HPA abnormalities. This line of research is important as it may have implications for the timing and nature of prevention interventions, which may differ depending on what the HPA axis anomaly is and when it manifests.

Overall, the findings reported in this dissertation suggest a pattern of relative continuity of risk across generations, defined by a trajectory of high emotionality and disagreeableness in the parents, offspring internalizing and externalizing problems in childhood, and interpersonal dysfunction in late adolescence and early adulthood. Our findings suggest that intervening early on high-risk families is of the utmost importance if we wish to prevent the development of this trajectory and interrupt the intergenerational transmission of affective disorders. In addition, high-risk status was found to be a moderator of the relationship between interpersonal stress and cortisol levels. This finding supports the view that an overly sensitive HPA axis in high-risk youth may underlie one aspect of the vulnerability to affective disorders. Importantly, the high cortisol levels exhibited by the OBD were attenuated in those reporting low levels of stress. This implies that the vulnerability associated with a family history of affective disorders may be mitigated by environmental interventions, which, once more, emphasized the promising benefits of prevention interventions in the OBD.

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