NEURAL CORRELATES OF RISK
IN CHILDREN OF PARENTS WITH BIPOLAR DISORDER
CHILDREN OF PARENTS DIAGNOSED WITH BIPOLAR DISORDER: AN INVESTIGATION OF THE BEHAVIOURAL, STRUCTURAL AND FUNCTIONAL CORRELATES OF RISK

By
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A Thesis Submitted to the School of Graduate Studies in Partial Fulfillment of the Requirements for a Degree of Doctor of Philosophy

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TITLE: Children of parents diagnosed with bipolar disorder: an investigation of the behavioural, structural and functional correlates of risk

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Abstract

Emotion processing and regulatory deficits have been well established in individuals diagnosed with bipolar disorder (BD). Both structural and functional neural deficits have been associated with the presence of psychiatric symptoms in BD. In Chapter 2, we reviewed cortical thickness deficits found in patients with BD. It is unclear however, how early these deficits appear; whether they contribute to risk, or whether these deficits develop as a consequence of the onset of symptoms.

To address this, many researchers have turned to high-risk offspring populations. These high-risk offspring are at much greater risk of developing BD by virtue of having a parent diagnosed with BD. Moreover, the presence of anxiety, depression or ADHD related symptoms in this population suggest these children are at even greater risk to develop BD. By comparing high-risk offspring with and without the symptoms can help to elicituate neural correlates associated with risk and resilience for BD. It was the aim of this thesis research to investigate the behavioural, structural and functional correlates of risk. Specifically, presented in this thesis, we compared the gray matter integrity, through volume (Chapter 3) and cortical thickness (Chapter 4) techniques, in symptomatic and asymptomatic high-risk offspring to healthy children of healthy parents. We also compared the ability of these offspring to perform an emotion-labelling task (Chapter 5) and engage in emotional conflict monitoring and conflict adaptation during an fMRI scan (Chapter 6).
Altogether, our results provide evidence for the presence of gray matter volume, emotion labelling, and conflict monitoring and conflict adaptation functional deficits in high-risk offspring compared to healthy children of healthy parents. With the exception of cortical thickness, we found that the deficits between symptomatic and asymptomatic high-risk offspring were comparable. This suggests that behavioural, structural and functional deficits may reflect neural correlates of risk and are not associated with the presence of symptoms.
Preface

My experience as a graduate student has been incredible. I have grown as a person in many capacities, for which, I have several people to thank.

To my family, thank you for all the love and support you have shown me along the way. To my parents, thank you for believing in me, and showing me that with a willing heart and dedication, anything is possible.

To my committee, I am thankful for all your feedback and for expanding my mind to the endless possibilities in research. To my supervisors, thank you for enriching my student experience through research opportunities, networking experiences and your invaluable mentoring. Dr. Sassi, thank you for pushing me to present this research at various scientific conferences, and for connecting me to wider research community, which has allowed me to find an exceptional post-doctoral associate position. Dr. Hall, thank you for your unending professional and personal support. I truly value all the advice you have given me over these past five years. Although my time as a graduate student is at an end, I look forward to working with both of you in the future.

And to my beloved husband, thank you for agreeing to share this life with me, for pushing me to be the very best I can be, and for being so supportive of my professional decisions. You are the best.
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<td>Anterior cingulate cortex</td>
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<td>ADHD</td>
<td>Attention deficit hyperactivity disorder</td>
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<td>BA</td>
<td>Brodmann’s area</td>
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<td>BD</td>
<td>Bipolar disorder</td>
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<tr>
<td>cC</td>
<td>Congruent trial followed by a congruent trial</td>
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<tr>
<td>cl</td>
<td>Congruent trial followed by an incongruent trial</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<td>CPRS</td>
<td>Connors parent rating scale</td>
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<td>DANVA</td>
<td>Diagnostic analysis of non-verbal accuracy</td>
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<td>FAHRO</td>
<td>Fully affected high-risk offspring</td>
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<td>fMRI</td>
<td>Functional magnetic resonance imaging</td>
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<td>GLM</td>
<td>General linear model</td>
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<td>HC</td>
<td>Healthy control</td>
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<td>HCO</td>
<td>Healthy control offspring</td>
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<tr>
<td>HRO</td>
<td>Healthy control offspring</td>
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<tr>
<td>iC</td>
<td>Incongruent trial followed by a congruent trial</td>
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<td>il</td>
<td>Incongruent trial followed by an incongruent trial</td>
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<td>IQ</td>
<td>Intelligence Quotient</td>
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<td>K-SADS-PL</td>
<td>Kiddie schedule for affective disorders present and lifetime</td>
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<td>OFC</td>
<td>Orbitofrontal cortex</td>
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<td>MASC</td>
<td>Multidimensional anxiety scale for children</td>
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<td>MDD</td>
<td>Major depressive disorder</td>
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<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<td>PAHRO</td>
<td>Partially affected high-risk offspring</td>
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<td>PRISMA</td>
<td>Preferred reporting items for systematic reviews and meta-analysis</td>
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<td>SCID</td>
<td>Structured clinical interview for DSM-IV</td>
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<td>Statistical parametric mapping</td>
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<td>Schizophrenia</td>
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<td>UAHRO</td>
<td>Unaffected high-risk offspring</td>
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<td>VBM</td>
<td>Voxel-based morphometry</td>
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<td>vlPFC</td>
<td>Ventrolateral prefrontal cortex</td>
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<td>WASI</td>
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Chapter 1
Introduction

Bipolar Disorder (BD) has been ranked as one of the most expensive medical conditions in North America as a consequence of its chronic and debilitating nature and its impact on both psychological and physical health (Goetzel, Hawkins, Ozminkowski, & Wang, 2003; Guilbert, 2003; Kleinman et al., 2003; Kupfer, 2005; Merikangas et al., 2011). BD affects 1-3% of persons globally and is characterized as a major mood disorder; with patients experiencing cycling of internal mood states of mania, depression and euthymia in any order (First, Spitzer, Gibbon, & Williams, 2012; Guilbert, 2003). These mood changes are often accompanied by other physical changes such as loss/increase in sleep, appetite and energy (First et al., 2012). Individuals diagnosed with BD report difficulty maintaining interpersonal relationships, employment and financial stability, and are often confronted with stigma surrounding BD (Dore & Romans, 2001; Michalak, Yatham, Maxwell, Hale, & Lam, 2007; Wahl, 1999). Moreover, individuals with BD have high rates of medical comorbidities, including hypertension, obesity, thyroid disease and/or diabetes, which may further increase their risk for adverse outcomes and reduce quality of life (Kilbourne et al., 2004; Krishnan, 2005; Sylvia et al., 2015). In addition, up to 40% of patients are often initially misdiagnosed (Bowden, 2005; Ghaemi, Boiman, & Goodwin, 2000; Ghaemi, Sachs, Chiou, Pandurangi, & Goodwin, 1999; Perugi et al., 2000; Xiang et al., 2013) with an average time of 6-10 years before a correct
diagnosis is reached (Ghaemi et al., 1999; Lish, Dime-Meenan, Whybrow, Price, & Hirschfeld, 1994; Morselli, Elgie, & GAMIAN-Europe, 2003). Investigating the underlying mechanisms of the disorder may result in the identification of biological markers that may improve the diagnostic accuracy and treatment of individuals living with BD.

It has been suggested that age of onset may distinguish subgroups within BD (Bellivier et al., 2003; Bellivier, Golmard, Henry, Leboyer, & Schürhoff, 2001; Schürhoff et al., 2000). While historically BD was considered an adult disorder, retrospective studies have suggested that as many as 60% of adults experience symptoms before 21 years of age (Bellivier et al., 2003; Bellivier et al., 2001; Goodwin & Jamison, 2007; Kessler et al., 2007; Kessler et al., 2005; Leboyer, Henry, Pailiere-Martinot, & Bellivier, 2005; Lish et al., 1994; Schürhoff et al., 2000). Further evidence has been provided by longitudinal offspring studies (Birmaher et al., 2010; Birmaher, Axelson, Monk, et al., 2009; Hillegers et al., 2005; Mesman, Nolen, Reichart, Wals, & Hillegers, 2014) which have also suggested that early onset is associated with familial risk, increased rates of comorbidity, poor response to treatment with lithium, and worse outcomes (Bellivier et al., 2003; Bellivier et al., 2001; Birmaher, Axelson, Goldstein, et al., 2009; McGlashan, 1988; Perlis et al., 2004; Schulze et al., 2002; Schürhoff et al., 2000; Strober et al., 1988). Although environmental risk factors may contribute to the development and progression of the disease, BD is known to have one of the highest heritability rates among psychiatric disorders (0.79-0.9) (Bienvenu, Davydow, & Kendler, 2011; Craddock, O’Donovan, & Owen, 2005; Dean et al., 2010; Kieseppa, Partonen, Haukka, Kaprio, &
Lonnqvist, 2004; McGuffin, Rijsdijk, & Andrew, 2003; Nurnberger et al., 2011; Wray & Gottesman, 2012). Therefore it follows that the study of biological factors in high-risk offspring populations, including brain structure and function, would be among the best avenues for discovering its aetiology.

Neuroimaging studies have helped to elucidate the neural pathways underlying BD. The general consensus model posits that both structural and functional deficits arise in emotional progressing and regulatory neural networks, and are thought to lead to the symptoms seen clinically (Blond, Fredericks, & Blumberg, 2012; Pavuluri, Passarotti, Harral, & Sweeney, 2009; Phillips, Ladouceur, & Drevets, 2008; Strakowski et al., 2012; Strakowski, Delbello, & Adler, 2005).

Specifically, there is a loss of top-down modulatory control of prefrontal cortical regions over limbic areas, including the amygdala (Blond et al., 2012; Pavuluri et al., 2009; Phillips et al., 2008; Strakowski et al., 2012; Strakowski et al., 2005). Structural imaging studies converge on decreased gray matter volumes and/or cortical thinning of the orbitofrontal (Elvsåshagen et al., 2013; Fears et al., 2014; Foland-Ross et al., 2011; Frangou, 2005; Hegarty et al., 2012; Lyoo et al., 2006; Makris et al., 2012; Narita et al., 2011; Nugent et al., 2006; Pol et al., 2012; Rimol et al., 2010), anterior cingulate (Drevets et al., 1997; Elvsåshagen et al., 2013; Farrow, Whitford, Williams, Gomes, & Harris, 2005; Foland-Ross et al., 2011; Fornito et al., 2008; Hegarty et al., 2012; Lyoo et al., 2006; Narita et al., 2011; Strakowski et al., 2005), ventral and dorsal prefrontal regions (Brooks et al., 2009; Elvsåshagen et al., 2013; Fears et al., 2014; Frangou, 2005; Hartberg et al., 2011; Hatton et al., 2013; Haznedar et al., 2005; Hegarty et al., 2012; Maller, Thaveenthiran, Thomson,
McQueen, & Fitzgerald, 2014). These regions can be placed at the heart of three neural networks responsible for managing emotional behaviours. Two of these networks are located in the ventral stream and are divided into two automatic processing pathways: (1) originating in the ventrolateral prefrontal cortex (vLPFC) important in the modulation of external emotional stimuli, and (2) originating in the ventromedial prefrontal cortex (also known as the orbitofrontal cortex OFC) involved in the modulation of internal emotional state. The third network (3) involves the dorsal stream, and is involved in the voluntary top-down control and regulation of emotion (dorsal regions of the prefrontal cortex) (Blond et al., 2012; Phillips et al., 2008; Strakowski et al., 2012; Strakowski et al., 2005; Townsend & Altshuler, 2012; Yamasaki, LaBar, & McCarthy, 2002). These networks, the ventral and dorsal pathways, are also known as the automatic and voluntary emotional regulatory pathways, respectively (Phillips et al., 2008; Strakowski et al., 2012). The anterior cingulate cortex (ACC) acts to integrate information from emotion (ventral) and cognitive (dorsal) functions of the prefrontal cortex, and has also been implicated in BD (Drevets, Savitz, & Trimble, 2008; Strakowski et al., 2012; Yamasaki et al., 2002). Functional neuroimaging studies in BD have identified decreased activation of the OFC (Blumberg, Leung, et al., 2003; Blumberg et al., 1999; Kronhaus et al., 2006; Townsend et al., 2013), ACC (Anand, Li, Wang, Lowe, & Dzemidzic, 2009; Townsend et al., 2013; Wang et al., 2009) and the vlPFC (Blumberg, Leung, et al., 2003; Foland et al., 2008; Foland-Ross et al., 2012; Townsend et al., 2013) and increased amygdala reactivity ((Almeida, Versace, Hassel, Kupfer, & Phillips, 2010; Altshuler et al., 2005; Sheline et al., 2001;
Yurgelun-Todd et al., 2000) reviewed by (C.-H. Chen, Suckling, Lennox, Ooi, & Bullmore, 2011)). Moreover, functional connectivity studies have revealed reduced inverse connectivity between the vIPFC and amygdala (Foland et al., 2008; Townsend et al., 2013), and the ACC and amygdala (Anand et al., 2009; Wang et al., 2009) in BD compared to healthy controls during emotion processing and resting state conditions.

The findings from structural imaging studies remain consistent across adult and pediatric populations, with one notable exception: (1) amygdala volume appears to be decreased in individuals diagnosed with pediatric BD (PBD) where as reports on amygdala volume in adults diagnosed with BD remain inconclusive (Blumberg et al., 2005; Blumberg, Kaufman, et al., 2003; Chang et al., 2005; W. J. Chen et al., 2004; DelBello, Zimmerman, Mills, Getz, & Strakowski, 2004; Dickstein, Milham, Nugent, & et al., 2005)(reviewed by (Usher, Leucht, Falkai, & Scherk, 2010)). Structural imaging studies in PBD that are consistent with adult studies are cited here (Dickstein et al., 2005; James et al., 2011; Paillère Martinot et al., 2013; Wilke, Kowatch, DelBello, Mills, & Holland, 2004). Increased amygdala activity is also reported in PBD populations (Brotman et al., 2010; Passarotti, Sweeney, & Pavuluri, 2010; Pavuluri, O’Connor, Harral, & Sweeney, 2008; Pavuluri, O’Connor, Harral, & Sweeney, 2007; Pavuluri et al., 2009; Rich et al., 2006). As well, increased activation of the ACC (Chang et al., 2004; Dickstein et al., 2007; Kim et al., 2012; Passarotti et al., 2010; Rich et al., 2010), OFG (Chang et al., 2004; Dickstein et al., 2007; Passarotti, Sweeney, & Pavuluri, 2011), and decreased activity in the vIPFC (Passarotti et al., 2011; Pavuluri et al., 2008; Pavuluri et al., 2007) are most
commonly reported. Taken together, although structural deficits in PBD are consistent with those found in adult BD, these same regions might be over-active during the early phase of the disorder and decrease over time. This increased function may be evidence of initial dysregulation of circuits or a compensatory mechanism at the onset of BD.

Studying high-risk offspring (HRO) populations can help reveal aberrant neurobiological markers that may exist before the onset of BD. As discussed previously, BD has high heritability rates, resulting in offspring of parents diagnosed with BD being at high-risk to develop not only BD (Birmaher, Axelsson, Monk, et al., 2009; Dean et al., 2010; Hillegers et al., 2005), but a variety of other mood, anxiety and/or behaviourally disruptive disorders (Birmaher et al., 2010; Birmaher, Axelsson, Monk, et al., 2009; Chang, Steiner, & Ketter, 2000; Henin et al., 2005; Hillegers et al., 2005; Nurnberger et al., 2011). Moreover, the trajectory for BD offspring with symptoms of depression, anxiety and/or ADHD at a young age is worse; they appear to be at highest risk for developing BD (Chang, Howe, Gallelli, & Miklowitz, 2006; Hajek et al., 2013). Studying HRO with and without psychiatric symptoms may help to determine why some offspring go on to develop BD and why some offspring remain resilient.

To date, there have been a number of structural and functional imaging studies investigating the neurobiological mechanisms of risk in HRO populations, however, the results are inconsistent. There is a strong need for discovering robust, reliable structural markers that remain consistent across a variety of methodologies. We posit that these differences may be attributed to the presence or absence of
symptoms. To help clarify, we have classified three HRO population types that differ on the presence of symptoms: (1) unaffected (UAHRO: these offspring are free of any psychiatric diagnoses), (2) partially affected (PAHRO: these offspring are diagnosed with or are subthreshold for a psychiatric disorder other than BD, including but not limited to ADHD, anxiety, and/or depression), and (3) fully affected (FAHRO: these offspring are diagnosed with BD). To date, no studies have compared these three offspring groups.

Structural imaging studies in HRO remain inconsistent; with few studies reporting increased gray matter volumes in the right amygdala (Bauer et al., 2014), head of the caudate (Hajek et al., 2009b) and left hippocampal/parahippocampal (Ladouceur et al., 2008) regions. Hajek and colleagues observed increased gray matter volume in the right inferior frontal gyrus in both unaffected and fully-affected HRO compared to HCO (Hajek et al., 2013). Unique to their study, these findings were replicated across two study centers (Hajek et al., 2013). Several studies also reported no significant differences between HRO and HCO populations in the following regions-of-interest: striatum (Bauer et al., 2014; Singh, DelBello, Adler, Stanford, & Strakowski, 2008), amygdala (Hajek et al., 2009a; Karchemskiy et al., 2011; Ladouceur et al., 2008; Singh et al., 2008), hippocampus (Bauer et al., 2014; Hajek et al., 2009a; Karchemskiy et al., 2011), thalamus (Karchemskiy et al., 2011; Singh et al., 2008), cingulate (Bauer et al., 2014; Hajek, Kozeny, Kopecek, Alda, & Hoschl, 2008; Hajek et al., 2010), and pituitary (Hajek, Gunde, et al., 2008). This absence of structural neurobiological deficits in unaffected high-risk offspring may be indicative of the action of neuroprotective factors.
Functional imaging studies in HRO have also been variable. Kim and colleagues found increased activity in the vIPFC and caudate, during a cognitive flexibility task, in unaffected first-degree relatives compared to a HC group (Kim et al., 2012). Theremenos et al. found increased activation in the OFC, insula and superior parietal, during a working memory task, in first-degree relatives with mood symptoms compared to HC group (Theremenos et al., 2010). Olsavsky et al. also studied first-degree relatives with ADHD or anxiety symptoms and reported increased activation of the right amygdala during implicit emotional-labelling task compared to HC group (Olsavsky et al., 2012). Deveney et al. found increased activation of the striatum during a motor inhibition task in unaffected first-degree relatives compared to HC group (Deveney et al., 2012). Roberts and colleagues reported a specific lack of recruitment of the inferior frontal gyrus in response to emotional go/no-go task in unaffected first-degree relatives (Roberts et al., 2013). Ladouceur et al. are one of the first and only research groups to report functional imaging results on an entirely unaffected HRO sample (Ladouceur et al., 2013). They found: (1) increased activation of the vIPFC during an emotional distracters working memory task in healthy HRO, and (2) decreased inverse functional connectivity between the vIPFC and amygdala in the HRO group (similar to PBD) (Ladouceur et al., 2013). Singh and colleagues reported a decreased connectivity between amygdala-ACC, ACC-supplementary motor cortex, and vIPFC-caudate on resting-state functional connectivity in unaffected HRO compared to HCO (Singh et al., 2014). Finally, Whalley et al. were able to distinguish those HRO who went on to develop depression by an increased activation of bilateral insular cortices, during an
executive function task, compared to the HCO group and those HRO who did not go on to develop depression (Whalley, Sussmann, Romaniuk, & Stewart, 2013). In summary, the majority of studies reported increased functioning in emotion processing related regions. These reports show some consistency with PBD studies, suggesting that both those at high risk for and those with PBD may experience an overactivation of emotion processing circuits that may result in an accelerated decline of function in adulthood. With further validation, this increased functioning may be used as a biological marker for at-risk and early stage BD. We further suggest this may be depicting a critical window of BD that could be used for targeted intervention. Further functional imaging results can help to validate these findings by minimizing methodological differences including recruitment of a study population with or without symptoms, risk from first-degree relatives with BD type I or type II, and/or task specific activation. A better management of methodological differences may help further our understanding of vulnerability factors and the core deficits related to psychopathology underlying BD.

Altogether, these findings help emphasize the need to find consistent, highly replicable biological markers for BD. We posit that previous discrepancies may, at least in part, be due to differences in the recruitment criteria for HRO. More specifically, this research program aimed to compare HRO, with and without symptoms, with HCO to reveal subtle neurobiological differences that may exist in these populations. We were interested in determining whether there are neurobiological protective mechanisms at work in unaffected high-risk offspring that are not present in partially-affected high-risk offspring that may help explain
outcome/developmental trajectories. Details of this research regime are described in more detail below.

The primary aim of this research program was to determine markers of risk that exist in HRO populations. Specifically, HRO with and without symptoms as well as HCO were recruited and asked to participate in structural and functional magnetic resonance imaging (MRI and fMRI) scans as well as an emotion labelling behavioural task outside the MR machine. Results of these components have been included in this thesis and contribute to a growing body of literature that suggests subtle differences exist in the neurocircuitry underlying emotion processing and regulation in children at high-risk to develop BD. In Chapter 2, a systematic review was conducted on all available literature concerning cortical thickness deficits in BD. Chapters 3 and 4 focus on gray matter integrity in HRO populations using gray matter volume and cortical thickness techniques, respectively. Finally, Chapters 5 and 6 describe emotion processing and regulation in HRO. Chapter 5 describes the results of an emotion labelling behaviour task including response patterns and error types that emerge between HRO populations. Chapter 6 describes the results of an emotional conflict task during a fMRI scan. This chapter describes the related neurocircuitry underlying emotion regulation. Lastly, Chapter 7 provides a summary of these findings, a general discussion on how these results contribute to our understanding of the neural correlates of risk and pathology in BD, and provides suggestions for future research avenues.
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Chapter 2

Cortical Thickness in Bipolar Disorder: A Systematic Review

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Abstract and Key Words

Objectives: Bipolar Disorder (BD) is a debilitating illness, the psychopathology of which is associated with aberrant structural and functional differences in the brain. Despite the many advances in psychiatric research, our understanding of the complex neurobiological underpinnings of BD remains incomplete. The aim of this review was to critically examine all available published magnetic resonance imaging (MRI) research reporting cortical thickness in BD with respect to a healthy population and/or other psychiatric samples.

Methods: The systematic search encompassed all relevant studies published until November 2014. Relevant papers were identified through an online search of select databases (MEDLINE and EMBASE) using key terms “bipolar disorder” or “mania”, and “cortical thickness”. Two independent raters determined the eligibility of papers and performed separate data extraction to ensure quality and accuracy of reporting.

Results: A total of 17 papers met criteria and were included in this review. Compared to a healthy population, the majority of studies reported decreased cortical thickness in left anterior cingulate/paracingulate, the left superior temporal gyrus, as well as several prefrontal regions bilaterally in patients with BD. Studies also show consistency of cortical thinning in individuals with BD and schizophrenia in frontal and temporal regions, suggesting some common neuropathology.

Conclusions: This systematic review further supports of the link between specific structural brain abnormalities and BD. Future studies should investigate cortical thickness with respect to at-risk populations to determine whether these neuropathologies develop before or after the onset of bipolar disorder.

Keywords
bipolar disorder – cortical thickness – MRI – biomarkers
Introduction

Bipolar disorder (BD) is a debilitating illness, the psychopathology of which is associated with aberrant structural and functional neural differences. Despite advances in psychiatric research, our understanding of the neurobiological underpinnings of BD remains incomplete.

Individuals with BD are often misdiagnosed during the early phases of the illness, as symptoms of BD overlap with other psychiatric disorders, most commonly major depressive disorder (1). Up to 40% of patients are initially misdiagnosed (1-5), with an average time of 6-10 years before a correct diagnosis is established (3, 6, 7). Misdiagnosis may lead to incorrect treatment interventions and numerous downstream consequences including increased risk of suicide, and/or the triggering of a manic episode (particularly when patients are treated with antidepressants or stimulants in the absence of mood stabilizer medications) (8-12). Investigating structural neural alterations associated with BD may result in a better understanding of the underlying mechanisms of the disorder, and may help to identify biological markers that can improve the diagnostic accuracy and treatment of individuals living with BD.

Although environmental risk factors may contribute to the development and progression of the disease, BD is known to have one of the highest heritability rates among psychiatric disorders (0.79-0.9) (13-19), suggesting that the study of
biological factors, including brain structure and function, would be among the best avenues for discovering its aetiology.

The integrity of cortical gray matter can be assessed by several methods. Generally, structural MRI studies define cortical gray matter as the gray matter contained between the pial surface and the gray/white matter border of the brain. Cortical gray matter can be quantitatively detailed through measures of volume, surface area and thickness. Cortical volume is the product of cortical thickness and cortical surface area. Both cortical thickness and cortical surface area are thought to directly measure the columnar organization of the cortex (20-22). While cortical surface area is reflective of the number of columns, which best represents the size of the cortex, cortical thickness measures reflect the number of cells within a column (represented as a vertex) and can therefore be thought of as a more spatially localized measure of these columns (20-24). Studies suggest that both cortical thickness and cortical surface area are highly heritable, and yet, these influences are unrelated (22-24). This suggests that a measure of cortical volume may be confounded by these unrelated genetic influences and therefore, either cortical surface area or cortical thickness methods would be advantageous in identifying a biological marker of BD (20, 22-24).

For this review, we therefore chose to focus on cortical thickness, as it reflects the most topographically conserved information about subtle gray matter changes. The best established non-invasive, MRI-based method for cortical thickness analysis
uses a surface-based representation of the cortex; a tessellated mesh or framework is created along the white matter boundary and pial surface that is used to calculate the shortest distance between these two surfaces (25-27).

Despite recent evidence demonstrating structural brain abnormalities in BD, to date, the literature related to cortical thickness in this population has not been systematically assessed. The objective of this systematic review is to assess and summarize the literature pertaining to cortical thickness analysis in BD.

**Methods**

This review was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines to ensure a high standard of reporting (28).

*Search Strategies*

Our literature search was conducted in November 2014. Two search strategies were implemented to ensure all relevant papers were included. First, online searches of MEDLINE and EMBASE databases were used to identify pertinent studies. In order for papers to be selected, they needed to include a combination of the following terms: *bipolar disorder* or *mania* and *cortical thickness*, or *cortical thinning*. Date of publication was not restricted, however, the search was restricted to only include human studies. For completeness, the reference list of papers that passed first and
second level inspection were screened for any other eligible studies (see Figure 1 for details).

*Study Selection*

Each article was required to pass a first- and second-level inspection to be included in this systematic review. This involved a title and abstract search and full text search, respectively. Article screening was conducted by two independent raters (LH and AN) using DistillerSR (www.systematic-review.net/) software. Articles meeting the following criteria were included in this review: (1) reported original findings, (2) used high-resolution MRI T1 weighted images, (3) involved human participants, (4) were published as a primary research article in a peer-reviewed journal, (5) used longitudinal, cross sectional, case-control or cohort study designs, (6) contained an BD participant group that was separate from all other diagnostic groups, (7) the comparison group was not genetically related to the BD participant group, and (8) contained cortical thickness as part of the analysis. Inter-rater agreement was assessed using Kappa scores at each level of inspection. Conflicts were discussed between two raters until an agreement was reached. Data extraction was conducted independently by the same raters, was consolidated, and tabulated for this review.

*Results*

The literature search resulted in ninety-five eligible papers, which were examined for duplicates (n=31) and relevance through two levels of screening (see Figure 1).
Twenty papers were removed during the title and abstract review due to these papers (1) not being primary research articles (n=7), (2) not containing a BD participant group (n=9), or (3) not including cortical thickness in the analysis (n=4). Twenty-eight papers were removed during the full-text review due to (1) not containing new/original data (n=11), (2) not containing an exclusive bipolar participant group (n=10), (3) not containing a genetically separate healthy control group (n=1) or (4) not including cortical thickness as part of the analysis (n=6). Finally, a review of the reference list of qualifying papers revealed one potential paper. Interrater reliability was considered very good (kappa= 0.825).

In total, seventeen papers met criteria and were included in this systematic review (29-45) (summarized in Tables 1-4). These included a combined total of 645 bipolar participants (BD: average age 33.9 ± 6.8 years, 59% female) and 888 healthy participants (HC: average age 33.4 ± 6.3 years, 51% female). We also chose to report other psychiatric groups if a direct comparison of cortical thickness was made to the bipolar group. These included seven papers comparing to 337 individuals with schizophrenia (SZ: average age 31.9 ± 6.0 years, 39% female) (29, 32, 35, 36, 38, 41, 44), 2 papers comparing 49 individuals with comorbid BD and Attention Deficit Hyperactivity Disorder (BD+ADHD: average age 35.8 ± 0.19 years, 39% female) (37, 39) and one paper comparing cortical thickness between BD to 56 individuals with unipolar depression (MDD: average age 36.9 ± 12.2 years, 57% female) (30). While medication information was missing from four studies (31-33, 44), the remaining studies reported that most bipolar participants were taking medication at the time
of the scan (most commonly lithium, antipsychotics and/or antidepressants). The percentage of bipolar participants who were not taking medication at the time of the scan ranged from 0 to greater than 50 percent. Most studies did not report on the mood state of the participants at the time of the scan. The majority of studies used a 1.5T MRI scanner, while the remaining studies used a 3T strength MRI scanner (16:5). Given the different in statistical power between whole-brain and region-of-interest (ROI) analyses, we chose to treat these types of studies separately. Eleven studies carried out whole-brain analyses (summarized in Tables 1 and 3) (30, 31, 33-38, 40, 41, 45) and the remaining seven studies used ROI analysis techniques (summarized in Tables 2 and 4) (29, 32, 39, 42-44, 46).

*Cortical thickness in BD compared to healthy control group*

The most consistently reported findings included reduced cortical thickness in BD patients in regions of the left cingulate, left temporal and bilateral frontal cortices compared to controls (see Figure 2).

Four whole-brain (34, 37, 40, 45) and two ROI (42, 43) studies reported altered cortical thickness in the left anterior cingulate region (BA24 and/or BA25). Fornito and colleagues were the only group to report increased cortical thickness of the right subgenual anterior cingulate of the BD group compared to the HC group, this findings was specific to males only (43). In this study, nearly all participants in the BD group were receiving typical/atypical antipsychotic treatment at the time of the scan (43), as compared to less than or roughly half the BD participants from other
studies. Increased volume of the anterior cingulate has been a previously reported artifact of antipsychotic medication exposure (47) and/or lithium exposure (48), which may explain the discordant findings of this paper. Another possibility suggested by the authors was that this finding might be related to a distinct neuroanatomical phenotype of BD with the onset of psychotic features. Six studies reported cortical thinning of the left paracingulate region (BA32)[ROI: (42), Whole-brain: (34, 37, 40, 41, 45)].

Six studies reported cortical thinning of the left superior temporal gyrus (BA22) [ROI: (32, 44), Whole-brain: (31, 34, 37, 41). Some whole-brain studies also reported more widespread cortical thinning across the temporal lobes (including regions of the temporal pole (BA38) (34, 37), middle temporal gyrus (BA21) (34, 37) and inferior temporal gyrus (BA20) (34, 37, 41). Three studies reported on cortical thickness of the parahippocampal gyrus (33, 38, 41). Bansal and colleagues found thinning of the left parahippocampal gyrus (33), Rimol et al, found thinning in the right parahippocampal gyrus (41), while Hulshoff Pol and colleagues found thinning bilaterally (38). Despite the interest in the parahippocampal gyrus, the current literature does not provide enough evidence to support this region as a biological marker for BD. One study reported widespread cortical thickening bilaterally on the lateral surfaces of the brain (33). This discordance may be attributed to a significant difference in tissue contrast across age in the BD and HC groups (BD<HC, p<0.0001) (33).
Eight of the eleven whole-brain studies reported cortical thinning in the superior frontal cortex (spanning Brodmann Area's 6, 8, 9, 10) (31, 33, 34, 37, 39-41, 45). Janssen and colleagues were one of the only ROI studies to investigate the frontal cortex, and reported mean cortical thinning in BD compared to HC (29). Several whole-brain studies also support decreased cortical thickness in the dorsolateral prefrontal cortex (Brodmann’s Areas 9 and 46) (30, 34, 45), the ventrolateral prefrontal/lateral orbitofrontal cortex (37, 38, 40, 41) and lastly, the medial orbitofrontal cortex (37-40, 45).

Comparison of deficits in BD type I and BD type II

Of the studies included in this review, nine studies reported on an entirely BD type I sample [ROI: (29, 32, 39, 42, 43), Whole-brain: (33, 36, 37, 40)] and only one study focused on BD type II (34). For those that sampled a combination of BD type I and II participants, four compared their findings across these BD subtypes (see Table 3 for details) (Whole-brain: (31, 35, 41, 45). Lyoo and colleagues reported no significant differences between BD groups in regions of cortical thinning between BD and HC. Alternatively, Rimol and colleagues found regions of decreased cortical thickness in BD type I compared to a HC group, however, these results disappeared when using a combined type I and type II BD group (41). Hatton et al. found differences in the overall effect size when comparing BD subtypes to a HC group and psychosis group (35). While the right fusiform showed a comparable small effect size across these subtypes, cortical thinning of the right supramarginal gyrus showed the largest (medium) effect size in BD spectrum disorder, while cortical thinning of the right
precuneus showed the largest (medium) effect size in BD type I compared to a HC group (35). Finally, most recently, Maller and colleagues showed two regions of differential cortical thickness between BD type I and II (31). Both the right medial orbitofrontal, and left superior temporal cortices were found to be thinner in BD type I as compared to BD type II (31).

_Cortical thickness in BD compared to other psychiatric groups_

Seven studies directly compared cortical thickness between BD and SZ participant groups (29, 32, 35, 36, 38, 41, 44). Reports from several studies suggested common cortical thickness alterations in BD and SZ groups in frontal and temporal regions including parahippocampal and fusiform gyrus (38, 41, 44). Hulshoff Pol and colleagues reported cortical thinning in the right orbitofrontal, bilateral parahippocampal and increased cortical thickness in the supramarginal, fusiform and pre- and post-central regions in both BD and SZ groups as compared to a healthy group (38). Rimol and colleagues also reported shared thinning in the orbitofrontal, superior frontal, superior and inferior temporal, parahippocampal and supramarginal regions compared to a healthy group (41). Lastly, Qiu and colleagues reported shared cortical thickness characteristics of the left planum temporale (44).

Some studies also report cortical thickness differences among BD and SZ groups; however, these reports were relatively inconsistent, providing further evidence of common pathological abnormalities. Ratnanather et al. reported that thickness
differences of the left planum temporale could discern healthy control, BD and SZ groups (32). Hatton et al. reported increased thickness of the right fusiform and left angular gyrus, and thinning of the right superior parietal cortices extending to the posterior cingulate in the BD group compared to the SZ group (35). Lastly, Qiu and colleagues found increased cortical thickness in the left inferior frontal, right middle and superior temporal cortices and the left cuneus compared to the SZ group (36). For many of these studies, the major focus was to determine the neural correlates of SZ compared to healthy and psychotic BD populations. The prevalence of psychotic symptoms in individuals with BD ranges from 20-50% (49-51). With suggested differences in illness trajectory and outcome for individuals with psychotic BD, there is potential for distinct underlying neural deficits when contrasting BD with psychosis to its non-psychotic counterpart (50-54). We suggest that future studies should disclose whether participants with BD are with or without psychotic symptoms.

Lan and colleagues compared the cortical thickness of individuals with BD and MDD (30). They reported the BD group showed significant cortical thinning in the right middle caudal frontal, left inferior parietal and right precuneus regions compared to MDD (30).

Lastly, two studies compared the interactive effects of a BD diagnosis with or without comorbid ADHD (ROI: (39), Whole-brain: (37)). Hegarty and colleagues reported cortical thinning in the left lateral orbitofrontal (BA 47) in the BD group
compared to the healthy group, however, this difference was diminished when comparing the BD comorbid with ADHD group to the healthy group (37). Makris and colleagues found that BD comorbid with ADHD did not have interaction effects, but rather, summative effects (the neural correlates of the comorbid condition were found to be the combination of the deficits seen in each condition separately) (39). These studies provide support for future studies to consider comorbid ADHD in their BD participant group as this does influence structural findings.

*Cortical thickness in BD and clinical variables*

A subset of studies chose to investigate cortical thickness correlations to various clinical variables (ROI: (29), Whole-brain: (30, 31, 34-36, 40, 41, 45)) (See Table 3 and 4 for more details). Reports of correlations between cortical thickness and duration of illness or age of onset were mostly non-significant (30, 34, 41) with some studies reporting negative correlations of illness duration or duration of illness to treatment onset to cortical thickness in the left paracingulate/medial prefrontal (40), left middle frontal (45) and right postcentral cortices (45). Foland-Ross and colleagues comment on the difficulty with disassociating duration of illness measures with nuisance regressors of age due to high colinearity between these variables (40). This study also found that thinning of the left orbitofrontal cortex was related to the number of depressive episodes, thinning of the left subgenual anterior cingulate was related to the number of hospitalized manic episodes and thinning of the left ventrolateral and dorsolateral prefrontal cortices
were correlated with a history of psychosis (40). Other investigated correlations included symptom severity (41) and family history (34), both were not significant.

Five studies investigated correlations of cortical thickness with well known clinical measures including the Hamilton Depression Rating Scale (HAM-D) (55), Global Assessment of Functioning (GAF) (56, 57), Positive and Negative Symptom Scale (PANSS) (58) and components of the neuropsychological cognitive battery from the Cambridge Automated Neuropsychological Testing Battery (59).

Maller et al showed negative correlations between HAM-D scores and cortical thickness in the right superior frontal and right superior temporal cortices (31), while Lan et al. showed no correlation within specified right caudal middle frontal, left inferior parietal and right precuneus regions (30). Janssen and colleagues reported that mean cortical thickness of the frontal, temporal, parietal or occipital lobes were correlated with GAF or PANSS scores (29). Meanwhile, using a whole-brain analysis Qiu et al. found that lower GAF was correlated with cortical thinning of the middle temporal gyrus (36). And finally, Hatton et al. reported a variety of positive correlations related to visual sustained attention and verbal learning and memory and cortical thickness in temporal and parietal regions (35).

**Discussion**

The aim of this systematic review was to examine all existing literature reporting a cortical thickness analysis in BD. In doing so, we were interested in examining how the available studies either converged or diverged in their findings, and whether any
important patterns in the available data would help advance our understanding of the illness. This review included 17 studies, the results of which converged on findings of decreased cortical thickness in several key regions involved in emotional processing and emotional regulatory regions: the left anterior cingulate, the superior temporal, bilateral superior frontal as well as several prefrontal regions bilaterally.

Several studies reported cortical thinning in the anterior cingulate and/or paracingulate regions (34, 37, 40-42, 45). Functionally, the anterior cingulate is responsible for attention, conflict monitoring, response inhibition and it contributes to the integration of direct and indirect emotional processing (60-68). These direct and indirect (cognitive) pathways are separated anatomically into ventral/rostral and dorsal/caudal regions of the anterior cingulate, respectively (69-71). Functional MRI studies suggest the ventral anterior cingulate cortex shows an increase in activation during manic state either during an emotional task or resting state (72-74). Similarly, Wang and colleagues suggested that abnormal connectivity of the ventral anterior cingulate cortex to the amygdala was associated with mania (75). Cortical thinning in these regions are in line with previous work suggesting decreased gray matter volumes in the subgenual anterior cingulate in individuals with BD (76, 77).

Widespread cortical thinning was also reported across the temporal lobes of patients with BD, including the superior, middle, inferior, parahippocampal, and
fusiform regions (31, 32, 34, 37, 38, 41, 44, 45). The superior temporal gyrus is a highly specialized region. The left superior temporal gyrus includes Wernicke’s Area, a region critical for processing language and speech, and bilaterally contains Heschl’s Area, an area important in auditory processing, and lastly, the Planum Temporale is responsible for multisensory integration including vision with audition (32, 78-81). Deficits in the superior temporal gyrus have been associated with a wide array of symptoms including auditory hallucinations (82, 83) and errors in facial emotion perception (84-88). The middle and inferior temporal gyri are involved in high-order visual processing (89). The inferior temporal gyrus includes the fusiform gyrus, a specialized region responsible for face recognition. It also houses important subcortical structures including the amygdala and hippocampus, and temporal connections to these regions are involved in processing and experiencing emotion (79, 81, 88).

The prefrontal cortex can be broadly divided along three functional pathways: (1) the dorsal stream; involving the dorsal anterior cingulate and dorsal regions of the prefrontal cortex, and is responsible for voluntary control and regulation of emotion, while the ventral stream can be further divided by the function of (2) processing emotional salient external cues; involving the ventrolateral prefrontal cortex, and (3) processing of internal mood state; involving the ventromedial and the orbital prefrontal cortices (69, 71, 90-92). The results of our review demonstrate consistent reports of widespread cortical thinning across regions
implicated in all three pathways. This thinning may reflect the emotional regulatory and emotion processing symptoms central to BD.

Dysfunction of frontal-striatal-thalamic neural network is thought to be central to emotional processing and regulation (69). This pathway is used to detect emotion and regulate emotion response through modulatory control of prefrontal cortical areas over the limbic system, including the amygdala (69, 90-94). Functional magnetic resonance imaging (fMRI) studies have reported decreased activity of the ventral prefrontal cortex specifically in individuals with BD (69, 90, 93, 95, 96). Similarly, the inferior frontal gyrus, has shown decreased activation in BD irrespective of mood state (93, 96). We posit there is enough evidence from functional and structural imaging studies to suggest decreased functioning of the prefrontal cortex may be associated with reduced cortical thickness (93, 94, 97, 98). As this relation can be complex, future studies would do well to examine the association between functional and structural abnormalities directly as this may help to elucidate the underlying pathology affecting these emotion-regulation circuits in BD.

To date, there is little support that cortical changes precede the onset of BD. Studying the first-degree relatives of patients diagnosed with BD can give insight to the biological and environmental predictors that may contribute to the development of a mental disorder as they are at greater risk of developing BD as well as other mood, anxiety, and/or disruptive behavior disorders (15, 99). A recent review
conducted by Fusar-Poli et al. reported on the results from 25 MRI and 10 fMRI studies investigating neural correlates in first or second-degree relatives of patients with BD (100). This review showed no significant differences in gray matter volumes, however, high-risk relatives showed an increase in activity of the superior and medial frontal gyri, as well as the left insula (100). This may suggest functional abnormalities precede the onset of BD, but structural abnormalities only appear after the onset of BD (100). A recent study by Fears and colleagues evaluated the genetic heritability of cortical thickness phenotypes (among others) for BD, and observed cortical thinning of the several frontal (lateral orbitofrontal, inferior frontal, rostral middle and superior frontal) and temporal (lingual, fusiform, superior and inferior temporal) regions were both heritable and associated with BD (46).

Our review also contrasted cortical thickness findings of BD to other psychiatric cohorts including SZ, MDD and the interaction between BD and comorbid ADHD. Our review suggests, at least in part, that some cortical thickness deficits are shared across BD and SZ diagnoses. This is in keeping with genetic, cognition and functional neuroimaging studies, and provides further evidence for shared neuropathology between BD and SZ (14, 101-104).

This review is not without limitations. Common to all reviews, our analysis was limited to the information reported in papers meeting our selection criteria. Most commonly, studies did not report information about comorbidities, psychotic
features or mood state of their BD participant group at the time of the scan. Information about mood state is critical for determining state versus trait biological markers. This review also provided evidence for the importance of considering comorbidities of BD such as psychosis or ADHD. While some studies did take into consideration the effects of medication, this was not always the case. Increased volumes of some brain regions have been a previously reported artifact of antipsychotic (47) and/or lithium (48) exposure. While this could be considered a limitation, the inclusion of medicated participants should more likely result in a loss of significant differences between BD and HC participant groups, and yet, this was not the case. Finally, there is no standard practice for reporting the results of cortical thickness analyses. Reported study observations ranged from uncorrected Pearsons correlation coefficients to corrected cohen’s d measures for effect size. Similarly, for whole-brain studies, peak or central standardized coordinates (X, Y, Z) were not commonly reported. This would have enabled us to perform meta-analytical techniques when the same brain region was reported in three or more of the included studies. We reported the findings with as much detail as possible and included specific gyri and Brodmann areas whenever possible. This limitation resulted in our figure (Figure 2) representing the best approximation of the reported clusters from each paper.

Conclusions
There is convincing evidence that structural abnormalities exist in BD in key emotional processing regions, in particular, the left anterior cingulate, left superior
temporal, bilateral superior frontal and widespread bilateral prefrontal regions. However, at this time, due to some inconsistency in findings, limited support for deficits found in first-degree relatives, and the overlap of findings with other psychiatric disorders (eg. MDD, SZ), we caution the use of cortical thickness as a biological marker for BD. Further research should consider the presence of psychotic symptoms, comorbidities, and mood state at the time of the scan to better understand their impact on cortical thickness in BD.
### Table 1 – Demographic and study characteristics of whole-brain analysis studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Assessment Instruments</th>
<th>BD Type</th>
<th>Illness Duration, years (SD)</th>
<th>Psychosis</th>
<th>Comorbidities</th>
<th>Group: # (% female) [average age in years (SD)]</th>
<th>Medications at Scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lan et al. (30)</td>
<td>2014</td>
<td>SCID, HAM-D, YMRS</td>
<td>I/II</td>
<td>20.1 (10.9)</td>
<td>NR</td>
<td>Anxiety (n=9), Eating Disorder (n=1), ADHD (n=2), Substance Use Disorder (n=11)</td>
<td>HC: 54 (48) [31.8 (10.5)] BD: 18 (50) [37.6 (9.6)] MDD: 56 (57) [36.9 (12.2)]</td>
<td>Benzodiazepines (n=NR)</td>
</tr>
<tr>
<td>Malli et al. (31)</td>
<td>2014</td>
<td>MINI, HAM-D</td>
<td>I/II/NOS</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>HC: 31 (55) [39.6 (10.8)] BD: 31 (65) [43.3 (8.1)]</td>
<td>NR</td>
</tr>
<tr>
<td>Bansal et al. (33)</td>
<td>2013</td>
<td>SCID, SADS-PL</td>
<td>I</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>HC: 58 (50) [27.7 (14.3)] BD: 38 (55) [32.2 (13.8)]</td>
<td>NR</td>
</tr>
<tr>
<td>Elvesashagen et al. (34)</td>
<td>2013</td>
<td>MINI, MADRS, YMRS</td>
<td>II</td>
<td>18.1 (6.8)</td>
<td>NR</td>
<td>Social Phobia (n=12), Panic Disorder (n=16), General Anxiety Disorder (n=2)</td>
<td>HC: 42 (60) [31.0 (9.1)] BD: 36 (72) [33.2 (8.6)]</td>
<td>Unmedicated (n=12), Lithium (n=1), Mood Stabilizers (n=15), Antidepressants (n=11), Antipsychotic Agents (n=4), Benzodiazepines (n=7)</td>
</tr>
<tr>
<td>Hatton et al. (35)</td>
<td>2013</td>
<td>BMRISINS, BPRS, HAM-D, YMRS</td>
<td>I/II/NOS</td>
<td>NR</td>
<td>None</td>
<td>ADHD (n=3)</td>
<td>HC: 49 (57) [24.2 (2.7)] BD: 73 (71) [21.9 (3.6)] SZ: 40 (28) [23.5 (3.4)]</td>
<td>Unmedicated (n=20), Mood Stabilizers (n=24), Antidepressants (n=21), Antipsychotics (n=41), Stimulants (n=2)</td>
</tr>
<tr>
<td>Qiu et al. (36)</td>
<td>2013</td>
<td>SCID, PANSS, YMRS</td>
<td>I</td>
<td>0.14 (0.11)</td>
<td>NR</td>
<td>BD+ADHD (n=18)</td>
<td>HC: 28 (54) [36.0 (10.9)] BD: 28 (54) [36.9 (11.8)] SZ: 28 (64) [35.8 (9.2)]</td>
<td>Mood Stabilizers (n=25), Antipsychotics (n=23)</td>
</tr>
<tr>
<td>Hegarty et al. (37)</td>
<td>2012</td>
<td>SCID, K-SADS, HAM-D, YMRS</td>
<td>I</td>
<td>NR</td>
<td>None</td>
<td>BD+ADHD (n=18)</td>
<td>HC: 31 (42) [37.8 (13.1)] BD: 17 (41) [39.3 (10.8)] BD+ADHD: 18 (39) [36.1 (13.3)]</td>
<td>BD/ BD+ADHD: Unmedicated (n=10), Antidepressants (n=11), Antipsychotic Agents (n=19), Benzodiazepines (n=1), Anticonvulsants (n=17), Stimulants (n=1)</td>
</tr>
<tr>
<td>Hulshoff Pol et al. (38)</td>
<td>2012</td>
<td>SCID, IDS, YMRS</td>
<td>I/II</td>
<td>11.3 (8.2)</td>
<td>NR</td>
<td>NR</td>
<td>HC: 164 (56) [37.6 (9.5)] BD: 62 (71) [40.1 (10.0)] SZ: 25 (44) [36.2 (11.0)]</td>
<td>Lithium (n=46), Antidepressants (n=17), Antipsychotics (n=6), Benzodiazepines (n=12)</td>
</tr>
<tr>
<td>Foland-Ross et al. (40)</td>
<td>2011</td>
<td>SCID, HAM-D, YMRS</td>
<td>I</td>
<td>19.8 (12.5)</td>
<td>50%</td>
<td>None</td>
<td>HC: 31 (42) [37.8 (13.1)] BD: 34 (38) [38.1 (12.0)]</td>
<td>Unmedicated (n=10), Antidepressants (n=9), Antipsychotics (n=17), Anticonvulsants (n=18), Benzodiazepines (n=1)</td>
</tr>
<tr>
<td>Rimol et al. (41)</td>
<td>2010</td>
<td>SCID, PANSS, IDS, YMRS</td>
<td>III</td>
<td>6.5 (6.5)</td>
<td>NR</td>
<td>NR</td>
<td>HC: 207 (48) [36.2 (9.7)] BD: 139 (62) [35.4 (11.3)] SZ: 173 (40) [32.3 (9.0)]</td>
<td>Unmedicated (n=18), Lithium (n=19), Antidepressants (n=48), Antipsychotic Agents (n=60), Anticonvulsants (n=51), Sedatives (n=13)</td>
</tr>
<tr>
<td>Lyoo et al. (45)</td>
<td>2006</td>
<td>SCID, HAM-D, YMRS</td>
<td>I/II</td>
<td>16.5 (11.5)</td>
<td>NR</td>
<td>None</td>
<td>HC: 21 (76) [31.5 (9.7)] BD: 25 (60) [33.8 (8.6)]</td>
<td>Unmedicated (n=7), Lithium (n=6), Depakote (n=4), Other (n=8)</td>
</tr>
</tbody>
</table>

BD= Bipolar Disorder, BD+ADHD= Bipolar Disorder comorbid with ADHD, BMRISINS= Brain and Mind Research Institute Structured Interview for Neurobiological Studies, BPRS= Brief Psychiatric Rating Scale, HAM-D= Hamilton Depression Rating Scale, HC= Healthy Control, IDS= Inventory of Depressive Symptoms, K-SADS= Kiddie Schedule for Affective Disorders and Schizophrenia, MADRS= Montgomery-Asberg Depression Rating Scale, MDD= Major Depressive Disorder, MINI= Mini-International Neuropsychiatric Interview, NR= Not Reported, PANSS= Positive and Negative Syndrome Scale, SCID= Structured Clinical Interview for DSM-IV, SD= Standard Deviation, SZ= Schizophrenia, YMRS= Young Mania Rating Scale.
Table 2 – Demographic and study characteristics of region-of-interest analysis studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Assessment Instruments</th>
<th>BD Type</th>
<th>Illness Duration, years (SD)</th>
<th>Psychosis</th>
<th>Comorbidities</th>
<th>Group: # (% female) [average age in years (SD)]</th>
<th>Controls</th>
<th>BD</th>
<th>Other</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janssen et al. (29)</td>
<td>2014</td>
<td>K-SADS-PL, PANSS, HAM-D,</td>
<td>I</td>
<td>NR</td>
<td>100%</td>
<td>NR</td>
<td>HC: S2 (38) [15.4 (1.5)] BD: 20 (35) [16.4 (1.6)] SZ: 20 (10) [15.8 (1.8)]</td>
<td>Lithium (n=4), Antidepressants (n=2), Antipsychotic Agents (n=20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ratnamather et al. (32)</td>
<td>2014</td>
<td>MINI/DIGS, SCAN/CIDI-SF</td>
<td>I</td>
<td>17.6 (12.7)</td>
<td>100%</td>
<td>NR</td>
<td>HC: 27 (47) [39.9 (11.1)] BD: 38 (56) [38.4 (15.6)] SZ: 31 (45) [41.4 (9.5)]</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Makris et al. (39)</td>
<td>2012</td>
<td>SCID, K-SADS</td>
<td>I</td>
<td>NR</td>
<td>NR</td>
<td>BD/BD+ADHD: Anxiety disorders (n=8), Substance use disorders (n=16)</td>
<td>HC: 23 (43) [34.6 (9.6)] BD: 18 (56) [39.9 (6.5)] BD+ADHD: 31 (39) [35.7 (12.0)]</td>
<td>BD/BD+ADHD: Unmedicated (n=9), Mood Stabilizers or Antipsychotic Agents (n=27), Antidepressants (n=33), Stimulants (n=11), Antianxiety (n=5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fornito et al. (43)</td>
<td>2009</td>
<td>SCID, PANSS</td>
<td>I</td>
<td>0.06 (range 0.01-2.26)</td>
<td>100%</td>
<td>NR</td>
<td>HC: 28 (38) [22.3 (3.9)] BD: 26 (38) [21.6 (1.2)]</td>
<td>Unmedicated (n=2), Lithium (n=7), Antipsychotic Agents (n=21)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fornito et al. (42)</td>
<td>2008</td>
<td>SCID</td>
<td>I</td>
<td>14.3 (10.2)</td>
<td>58%</td>
<td>NR</td>
<td>HC: 24 (71) [38.7 (11.1)] BD: 24 (71) [39.5 (10.5)]</td>
<td>Unmedicated (n=4), Lithium (n=12), Mood Stabilizer (n=12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Qiu et al. (44)</td>
<td>2008</td>
<td>DIGS/Mini, SCAN/CIDI-SF</td>
<td>NR</td>
<td>NR</td>
<td>100%</td>
<td>NR</td>
<td>HC: 20 (50) [36.5 (11.0)] BD: 20 (50) [36.5 (8.0)] SZ: 20 (50) [36.5 (8.0)]</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BD= Bipolar Disorder, BD+ADHD= Bipolar Disorder comorbid with ADHD, CIDI-SF= Composite International Diagnostic Interview- Short Form, DIGS= Diagnostic Interview for Genetic Studies, HAM-D= Hamilton Depression Rating Scale, HC= Healthy Control, K-SADS= Kiddie Schedule for Affective Disorders and Schizophrenia, MINI= Mini-International Neuropsychiatric Interview, NR= Not Reported, PANSS= Positive and Negative Syndrome Scale, SCAN= Schedule for Clinical Assessment of Neuropsychiatry, SCID= Structured Clinical Interview for DSM-IV, SD= Standard Deviation, SZ= Schizophrenia, YMRS= Young Mania Rating Scale.
Table 3 – Summary of structural imaging findings of whole-brain analysis studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>BD State</th>
<th>Software Pipeline</th>
<th>Multiple Comparisons</th>
<th>Testa</th>
<th>Kernel</th>
<th>Results</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lan et al. (30)</td>
<td>2014</td>
<td>Depressed</td>
<td>Freesurfer</td>
<td>Monte Carlo 10 000 iterations</td>
<td>3</td>
<td>10 mm</td>
<td>Decreased CT in the right caudal middle frontal (1.0e-4), right posterior cingulate (0.018), bilateral inferior parietal (L:1.0e-4, R:0.002), left superior parietal (0.018), right supramarginal (0.037) regions (BD&lt;HC). Decreased CT in the right caudal middle frontal (1.0e-4), left inferior parietal (0.021) and right precuneus (0.023) compared to MDD (BD=MDD). Decreased CT in the left inferior parietal (1.0e-4), bilateral superior frontal (L:1.0e-4, R:1.0e-4), right superior parietal (1.0e-4,0.0-3), right precuneus (1.0e-3), right medial orbital frontal (0.024), right fusiform (0.035) regions (BD=MDD). No significant correlations between CT and HAMD D scores or age of onset of illness for the right caudal middle frontal, left inferior parietal or right precuneus regions (BD).</td>
<td>Two-tailed Student T-test; one way ANOVA with Bonferroni correction. Cluster-wise p values presented here.</td>
</tr>
<tr>
<td>Makler et al. (31)</td>
<td>2014</td>
<td>Depressed</td>
<td>Freesurfer</td>
<td>Monte Carlo thresholded for 1.3 (p&lt;0.05)</td>
<td>1.5</td>
<td>10 mm</td>
<td>Decreased CT in the right superior frontal (0.018), left superior (1.0e-4) and inferior parietal (1.0e-4), right supramarginal (4.0e-3), right precuneus (5.0e-4), right pars opercularis (3.0e-4) regions (BD&lt;HC). Decreased CT in the right thalamus cingulate (1.0e-4), left inferior parietal (1.0e-4) (BD&lt;HC), and increased CT in the left posterior transcallosal (1.0e-4) regions (BD=HC). Decreased CT in the right superior frontal (4.8e-3), right superior temporal (0.015), right transverse temporal (0.04), right precuneal (0.04) regions (BD&lt;HC). Decreased CT in the right medial orbitofrontal (0.021) and left superior temporal (4.0e-4) regions (BD=BDI). Negative correlations between CT and HAMD D scores in the right superior frontal (4.0e-4) and right superior temporal (0.047) in the BD group.</td>
<td>One and two tailed Student T-tests were applied. Cluster-wise p values presented here.</td>
</tr>
<tr>
<td>Bansal et al. (33)</td>
<td>2013</td>
<td>NR</td>
<td>Freesurfer/SPM5</td>
<td>NR</td>
<td>1.5</td>
<td>NR</td>
<td>Decreased CT in the bilateral superior frontal, and left parahippocampal regions (BD&lt;HC), general brain-wide increase in CT including lateral frontal, temporal, lateral parietal, lateral occipital regions (BD&lt;HC).</td>
<td>Cluster-wise p values presented here.</td>
</tr>
<tr>
<td>Elvassenagen et al. (34)</td>
<td>2013</td>
<td>Depressed</td>
<td>Freesurfer</td>
<td>Monte Carlo 10 000 iterations</td>
<td>3</td>
<td>20 mm</td>
<td>Decreased CT in two clusters comprised of the left ventromedial prefrontal (BA 10/33), left subgenual anterior cingulate (BA 24/25), bilateral dorsomedial prefrontal (BA 9/10/24/32), and one cluster comprised of the left superior, middle and inferior frontal (BA 24/32), 21, 20,(0.0-3) regions (BD&lt;HC). No significant correlations between CT and illness duration, mood state or family history (BD=HC). Those BD patients taking medications has less severe CT deficits in prefrontal regions than those BD patients not taking medications (BDmed=BDnonmed).</td>
<td>Effect size, Cohen’s d presented here.</td>
</tr>
<tr>
<td>Hatton et al. (35)</td>
<td>2013</td>
<td>NR</td>
<td>Freesurfer</td>
<td>uncorrected p&lt;0.001</td>
<td>3</td>
<td>15 mm</td>
<td>Decreased CT in the right precuneus (0.18), left calcarine (0.35), right supramarginal (0.08) and right preceneral (0.11) regions (BD&lt;HC). Increased CT in the right fusiform (0.28), left angular (0.36-0.43)(BD&lt;SD2), and decreased CT in the right parieto-occipital sulcus to ventral posterior cingulate (0.08) regions compared to SZ (BD&lt;SD2=HC). Decreased CT in the right precuneus (0.26)(BD&lt;SD2) and right superior temporal (0.04)(SDNOS=HC) and increased CT in the right supramarginal regions (0.44)(BDNOS=SD). Correlations of decreased CT in left angular, right superior temporal, and right supramarginal were related to worse performance on visual sustained attention, verbal fluency, and verbal learning and memory (BDI). Correlations of decreased CT in the right superior temporal were related to worse performance on visual sustained attention, left posterior angular and right precuneus to increased performance on verbal fluency and right calcarine to increased performance on episodic memory and learning (BDI).</td>
<td>Cluster-wise p values presented here.</td>
</tr>
<tr>
<td>Gii et al. (36)</td>
<td>2013</td>
<td>NR</td>
<td>Freesurfer</td>
<td>Random Field Theory, vertex threshold of p&lt;0.01, cluster threshold of p&lt;0.05</td>
<td>3</td>
<td>30 mm</td>
<td>Decreased CT in the left lingual (BD&lt;HC), Increased CT in the right middle temporal (BD&lt;HC). Increased CT in left inferior frontal, right middle temporal, left cuneus regions (BD&lt;SD2). Correlated with decreased CT in the middle temporal gyms with lower SAD (p&lt;0.24, p=0.039) (BD).</td>
<td>NR</td>
</tr>
<tr>
<td>Hegarty et al. (37)</td>
<td>2012</td>
<td>Euthymic</td>
<td>3D Eikonal</td>
<td>Permutation correction, 10 000 iterations</td>
<td>1.5</td>
<td>15 mm</td>
<td>Decreased CT in bilateral orbitofrontal (BA14/15/3, 2, 3), right ventrolateral prefrontal (BA 14/30), right frontal pole (BA10/12, 0.01, 0.04), bilateral dorosmedial prefrontal (BA 8/18/19/30, 0.03), left inferior parietal (BA 38/20), left angular (BA20/30), left supramarginal (BA40/01), right occipital (BA18/19), (0.01,0.01) regions (BD=HC). Decreased CT in the left lateral orbitofrontal (BA 47/37/5/05) (BD=BD+ADHD).</td>
<td>Cluster-wise p values presented here.</td>
</tr>
<tr>
<td>Hutnikov Po et al. (38)</td>
<td>2012</td>
<td>Euthymic</td>
<td>CIVET pipeline, 3D Eikonal</td>
<td>Uncorrected p&lt;0.001</td>
<td>1.5</td>
<td>20 mm</td>
<td>Decreased CT in the bilateral orbitofrontal, bilateral parahippocampal, right medial orbitofrontal, right medial occipital calcarine (BD&lt;SD2HC), and increased CT in the left supramarginal, left fusiform, bilateral prefrontal and right postcentral regions (BD&lt;SD2HC).</td>
<td>Correlations to genetic or environment influences, raw p values not reported.</td>
</tr>
<tr>
<td>Poland-Ross et al. (40)</td>
<td>2011</td>
<td>Euthymic</td>
<td>Freesurfer</td>
<td>Monte Carlo thresholded for 1.3 (p&lt;0.05)</td>
<td>1.5</td>
<td>15 mm</td>
<td>Decreased CT in the bilateral orbitofrontal (BA 11/12/18), bilateral dorsomedial prefrontal (BA 8, left BA 9), 0.046, trend 0.071, R trend 0.05, left ventrolateral prefrontal (BA 44/01), left frontal pole (BA 10/02), left anterior cingulate (BA 24/32), 0.04, regions (BD=HC). Significant negative correlations between duration of illness and CT in the left medial orbitofrontal (BA 24, 43, 8, 1.5, 17, 5, 13, 0.3, p=0.05), between interval between illness onset and treatment onset and CT in the left paracingulate/medial prefrontal (BA 24, 32, 8) F=4.17, df=1,1.0, p=0.05, number of depressive episodes and CT in the left orbitofrontal cortex (BA 8, 11, 10) F=4.17, df=1,1.0, p=0.05) and a positive correlation between number of hospitalizations for mania and CT in the left subgenual anterior cingulate (BA 25/45, 21, 12, 0.03) (BD&lt;HC). Significant negative correlations of psychosis and decreased CT in the left ventrolateral (BA 24/32), 0.047, df=1,1.29, p=0.041) and left dorsolateral prefrontal cortex (F=4.2, df=1,1.29, p=0.05) and left temporal pole (F=8.43, df=1,1.29, p=0.007).</td>
<td>Two-tailed T-Test</td>
</tr>
<tr>
<td>Rimol et al. (41)</td>
<td>2010</td>
<td>NR</td>
<td>Freesurfer</td>
<td>False Discovery Rate p&lt;0.05</td>
<td>1.5</td>
<td>30 mm</td>
<td>NSD (BD=HC). Decreased CT in the left orbitofrontal, right superior frontal, right posterior superior temporal, right inferior temporal, right parahippocampal, bilateral inferior parietal, right supramarginal, bilateral occipital regions (BD&lt;HC). NSD (BD=SD2). No significant correlations between CT and duration of illness or symptom severity (BD).</td>
<td>NR</td>
</tr>
<tr>
<td>Lyoo et al. (45)</td>
<td>2006</td>
<td>NR</td>
<td>Freesurfer</td>
<td>uncorrected p&lt;0.001</td>
<td>1.5</td>
<td>NR</td>
<td>Decreased CT in the left dorsolateral prefrontal (BA 13/15), right orbitofrontal (BA 10), left anterior (BA 24/23) and posterior (BA 23) cingulate, left medial orbitoc (BA 18), right angular (BA 34), right fusiform (BA 19), and bilateral postcentral (BA 34) regions (BD&lt;HC). NSD (BD = BDI). Correlation of decreased CT in the left middle frontal cortex (r=0.38,p=0.06-3) and right postcentral cortex (r=0.45, p=0.04) with increased duration of illness (BD).</td>
<td>Independent T-test, all p&lt;0.001.</td>
</tr>
</tbody>
</table>

BA= Brodman’s Area, BD= Bipolar Disorder, CT= Cortical Thickness, HC= Healthy Control, MDD= Major Depressive Disorder, NR= Not Reported, NSD= No Significant Differences, SZ= Schizophrenia.
**Table 4 – Summary of structural imaging findings of region-of-interest analysis studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>BD State</th>
<th>ROIs</th>
<th>Software Pipeline</th>
<th>Multiple Comparisons</th>
<th>Tesla</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janssen et al. (29)</td>
<td>2014</td>
<td>NR</td>
<td>Frontal, Temporal, Parietal, Occipital</td>
<td>Freesurfer</td>
<td>False Discovery Rate</td>
<td>1.5</td>
<td>Decreased CT in the frontal cortex (d=0.5, r=0.24) (BD&lt;HC). No significant correlations between CT and CGAF or PANSS (BD).</td>
</tr>
<tr>
<td>Ratnanather et al. (32)</td>
<td>2014</td>
<td>NR</td>
<td>Superior Temporal Sulcus, Planum Temporale</td>
<td>Labeled cortical distance mapping</td>
<td>Holm's correction</td>
<td>1.5</td>
<td>Decreased CT in the left planum temporale (d=-0.015, r=-7.5e-3)(HC&gt;BD&gt;SZ).</td>
</tr>
<tr>
<td>Makris et al. (39)</td>
<td>2012</td>
<td>NR</td>
<td>32 ROIs</td>
<td>Freesurfer</td>
<td>NR</td>
<td>1.5</td>
<td>Increased CT in the left posterior cingulate (BA 23)(d= -0.9, r= -0.41), right middle temporal (d= -0.33, r= -0.16), right angular (BA 39)(d= -0.81, r= -0.37), bilateral fusiform (BA 37)(L:d=-0.32, r= -0.16, R:d= -0.74, r= -0.35), right posterior insula (d= -0.8, r= -0.37), right lateral occipital (BA 18/19)(d=0.44, r=0.21) regions (BD&gt;HC). Decreased CT in the right prefrontal (BA 9/10/11)(d=0.59, r=0.28) region (BD&lt;HC). NR (BD=BD+ADHD).</td>
</tr>
<tr>
<td>Fornito et al. (43)</td>
<td>2009</td>
<td>Psychotic</td>
<td>Paracingulate, Anterior Cingulate Cortex</td>
<td>Freesurfer</td>
<td>Bonferroni correction</td>
<td>1.5</td>
<td>Increased CT in the right subcallosal anterior cingulate in males only (d=-0.66, r= -0.39)(BD&gt;HC).</td>
</tr>
<tr>
<td>Fornito et al. (42)</td>
<td>2008</td>
<td>NR</td>
<td>Dorsal, Rostral and Subcallosal Anterior Cingulate Cortex</td>
<td>Freesurfer</td>
<td>Bonferroni correction</td>
<td>1.5</td>
<td>Decreased CT in the left rostral (d= -0.72, r= -0.34) and right dorsal (d= -0.59, r= -0.29) paracingulate and trend for decreased CT in the left dorsal paracingulate regions (BD&lt;HC) and trend for increased CT in the left rostral anterior cingulate (BD&gt;HC).</td>
</tr>
<tr>
<td>Qiu et al. (44)</td>
<td>2008</td>
<td>NR</td>
<td>Left Planum Temporale</td>
<td>Local labelled cortical mantle distance mapping</td>
<td>FDR/RFT</td>
<td>1.5</td>
<td>Increased CT in the posterior portion (BD=SZ&lt;HC), decreased CT in the anterior portion of left planum temporal regions (BD=SZ&lt;HC), NSD in mean CT (BD=SZ&lt;HC).</td>
</tr>
</tbody>
</table>

BA= Brodman's Area, BD= Bipolar Disorder, CT= cortical thickness, d= cohen's d for effect size, HC= Healthy Control, MDD= Major Depressive Disorder, NR= Not Reported, NSD= No Significant Differences, ROIs= Regions of Interest, SZ= Schizophrenia.
Figure 1 - Summary of the selection process used to identify articles eligible for inclusion in this systematic review.
**Figure 2** – Cortical map representing the approximate locations of reported differences in cortical thickness between bipolar and healthy control groups. Red represents regions of increased cortical thickness in bipolar group. Blue represents regions of decreased cortical thickness in bipolar group. Here we see the majority of reports cluster in the left cingulate, left superior temporal and bilateral prefrontal regions.
Disclosures
Dr. Sassi receives consultant and speaker support from BMS, Jansen. The remaining authors of this paper do not have any commercial associations that might pose a conflict of interest in connection with this manuscript.

Author Contributions
L.C.H., G.B.H. and R.B.S. were responsible for the study design. L.C.H. was responsible for the collection, interpretation of results, and preparation of the manuscript. L.C.H. and A.N. carried out the systematic review. All authors contributed to the provided feedback, including edits and conceptual feedback, on the manuscript at all stages.

References


Chapter 3

Gray Matter Volumes in Symptomatic and Asymptomatic Offspring of Parents Diagnosed with Bipolar Disorder

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Abstract and Keywords

Introduction: Children of parents diagnosed with bipolar disorder (BD), termed high-risk offspring (HRO), are at greater risk of developing BD over their lifetime. Previous studies have observed gray matter volume abnormalities in HRO compared to healthy children of healthy parents (HCO), however, these reports are inconsistent. We posit that the variability in results may be attributed to differences in methodology among offspring studies, in particular the presence of psychiatric symptoms in HRO. It was the aim of this study to directly compare gray matter volumes between symptomatic and asymptomatic HRO, and HCO.

Methods: High-resolution T1-weighted MR images were collected from 31 HRO (18 symptomatic and 13 asymptomatic) and 20 age- and sex-matched HCO. HRO were required to have at least one parent diagnosed with BD. Symptomatic HRO were defined as having a psychiatric diagnosis other than BD, while asymptomatic HRO were required to be free of any psychiatric diagnosis. These images were processed using voxel-based morphometry methods and between group analyses were performed in SPM.

Results: Compared to HCO, the combined HRO group showed decreased gray matter volumes in the right inferior orbitofrontal, right middle frontal, and bilateral superior and middle temporal regions. Both symptomatic and asymptomatic HRO groups showed gray matter volumes in these regions separately when compared to HCO. When comparing symptomatic and asymptomatic HRO, gray matter volumes were comparable in all regions except the lateral occipital cortex.

Conclusions: Our study was the first to compare symptomatic and asymptomatic HRO directly. In doing so, we provided further support for the presence of deficits in HRO, and confirmed that these deficits are present irrespective of the presence of symptoms in HRO.

Keywords
Bipolar offspring – high-risk offspring – bipolar disorder – gray matter volumes – voxel-based morphometry - MRI
**Introduction**

The investigation of first-degree relatives of patients diagnosed with bipolar disorder (BD) has become a popular avenue for examining factors that contribute to risk for the disorder. In particular, children of parents diagnosed with BD have been a target sample for many neuroimaging studies. Because BD is highly familial \(^1\)\(^-\)\(^8\), children of parents diagnosed with BD, termed high-risk offspring, are at greater risk of developing BD during the course of their lifetime \(^3\)\(^,\)\(^8\)\(^,\)\(^9\). Moreover, those offspring who develop symptoms of ADHD, anxiety, and/or depression in childhood appear to be the most vulnerable to develop BD \(^10\)\(^-\)\(^12\). A better understanding of the neurobiological mechanisms underlying risk in this population could help not only to further our understanding of BD, but may help to determine which offspring may go on to develop BD and which offspring will remain resilient.

Our current understanding of the neurocircuitry underlying BD involves dysfunction of the fronto-striatal-limbic pathway \(^13\)\(^-\)\(^17\). This pathway ascertains that prefrontal regions, such as the orbital prefrontal cortex, have a pivotal role in the down regulation of more primitive limbic regions, including the amygdala. The prefrontal cortex can divided along three emotion related regulatory pathways: (1) the ventral stream is involved in automatic processing of internal mood state (orbitofrontal and ventromedial prefrontal cortices), as well as (2) the automatic processing of external emotionally-salient stimuli (ventrolateral prefrontal cortex), and (3) the dorsal stream is involved in the voluntary control and regulation of emotion (dorsal regions of the prefrontal cortex) \(^13\)\(^-\)\(^15\)\(^,\)\(^17\)\(^,\)\(^18\). It has been well
established that the amygdala plays an important role in the emotional processing of faces and the detection of threat. In BD, both reduced activation of frontal regions as well as a hyperactivation of limbic regions are thought to contribute to a loss of top-down modulatory control over the limbic system. This dysfunction is thought to lead to emotional dysregulation and mood changes seen clinically in BD. While our understanding of this pathway has become clear, it remains unclear which deficits exist early on that may lead or contribute to the vulnerability for BD.

To date, many high-risk offspring studies have examined whether gray matter volume abnormalities exist in this population, however, the results are inconsistent. There is a strong need for discovering robust, reliable structural markers that remain consistent across a variety of methodologies. We posit that these differences may be attributed to the presence or absence of symptoms in high-risk offspring populations. To help clarify, we have defined three high-risk offspring population types and that differ on the presence of symptoms: (1) unaffected (UAHRO: these offspring are free of any psychiatric diagnoses), (2) partially affected (PAHRO: these offspring are diagnosed with psychiatric disorders other than BD, including but not limited to ADHD, anxiety, and/or depression), and (3) fully affected (FAHRO: these offspring are diagnosed with BD). To date, no studies have compared these three offspring groups.

By examining UAHRO populations, studies are able to examine gray matter abnormalities related to risk as this is before the onset of any psychiatric disorders.
One disadvantage of sampling this population is the potential for modelling an entirely resilient population, however, the discovery of resiliency factors can be just as informative. Previous studies have observed comparable gray matter volumes in the striatum\textsuperscript{20,21}, subgenual anterior cingulate\textsuperscript{22,23}, and pituitary regions\textsuperscript{24} in UAHRO and healthy children of healthy parents (HCO). Alternatively, reports have been conflicted for regions of the amygdala (increased\textsuperscript{25,26}, no significant difference\textsuperscript{20,21}), and hippocampus (increased\textsuperscript{25}, no significant difference\textsuperscript{20}). One recent study reported increased gray matter volume in the right inferior frontal gyrus for both UAHRO and FAHRO compared to HCO\textsuperscript{27}. This finding was supported in part by a previous study which found a trend of increased volume in UAHRO in this region\textsuperscript{25}.

Studies on PAHRO have been minimal\textsuperscript{21,28}. This may be due to the difficulty in discerning deficits related to illness burden from deficits related to risk/vulnerability. These studies observed comparable volumes in the amygdala, thalamus, striatum, hippocampus and prefrontal cortices\textsuperscript{21,28}.

Lastly, the results of gray matter volume differences in FAHRO compared to HCO have been inconsistent. Some studies have observed comparable brain volumes in the striatum\textsuperscript{21,29,30}, hippocampus\textsuperscript{20,29} and subgenual anterior cingulate\textsuperscript{22,23}. One study observed reduced hippocampal volume with increased anxiety scores\textsuperscript{31}. Reports have been inconsistent with amygdala volumes in FAHRO (decreased\textsuperscript{29}, no significant differences\textsuperscript{20,21,26}). One study reported increased volume of the right inferior frontal gyrus which was confirmed across two independent study
populations 27. There have also been reports of decreased volume in the lateral orbital frontal, right inferior frontal and superior temporal cortices 32. Other neuroimaging studies in pediatric and adult BD have suggested decreased volumes in the superior temporal 33,34, middle and inferior temporal 35-37, orbital frontal 34-38, as well as other dorsal and ventral prefrontal regions 34-36,39.

In summary, gray matter volume abnormalities appear to be present in high-risk offspring and may relate to the neurobiological circuitry underlying risk for BD. Currently, gray matter deficits remain inconsistent and this may be attributed to differences in methodology including the recruitment criteria of HRO populations. Here, we compare UAHRO and PAHRO to determine if symptom presence plays a role in the existence of these deficits. In doing so, we plan to compare deficits that may related to risk/vulnerability and others that may relate to resilience. Based on previous work, we predict to find decreased gray matter volumes in prefrontal regions including the orbitofrontal cortex, as well as increase in volumes in the UAHRO group in the parahippocampal and inferior frontal regions. We expect that gray matter volume deficits will be worse in those offspring that present with symptoms compared to unaffected HRO due to both vulnerability and increased illness burden.
Methods

Participants and Clinical Assessments

The Hamilton Integrated Research Ethics Board approved this research protocol. After a complete description of the study, written consent and assent were obtained from parent and child. High-risk offspring (HRO) were defined as having at least one biological parent diagnosed with BD, while healthy offspring (HCO) were required to be free of psychiatric disorders and have no family history of any psychiatric disorders within their first-degree relatives. The Kiddie Schedule for Affective Disorders Present and Lifetime (K-SADS-PL) diagnostic interview was used to assess subthreshold symptoms, past and/or current diagnoses in all participants. This information was used to confirm the absence of any psychiatric disorders in HCO, as well as further categorize HRO into partially-affected (PAHRO: those offspring who were subthreshold or met criteria for a diagnosis) and unaffected (UAHRO: those offspring who were free of any psychiatric symptoms). The Structured Clinical Interview for DSM-IV (SCID) was used to confirm a diagnosis of BD (Type I or II) in HRO parents and to confirm the absence of psychiatric disorders in parents of the HCO group. All participants were recruited between the ages of 8 and 16 years, and were excluded if they met any of the following criteria: a lifetime or current diagnosis of a pervasive developmental disorder, a substance use disorder, a neurological condition, an intelligence quotient (IQ) of less than 70, or the presence of any contraindications for an MRI scan. Trained clinical nurses conducted all interviews and all diagnoses were reviewed by a board certified child psychiatrist (RBS).
**Data Acquisition**

As part of the study protocol, all participants were introduced a mock scanner. This was to help participants become better acquainted with the sights and sounds of the MRI and to improve image quality by reducing the amount of movement during the scan. All images were collected using a General Electric 3T whole-body short-bore scanner (Milwaukee, WI) at St. Joseph's Healthcare Hamilton (Hamilton, Ontario). A 3D spoiled gradient recall pulse sequence was used to collect high-resolution T1-weighted images (repetition time = 10.8ms, echo time = 2ms, flip angle = 20, field of view = 240mm, 256 x 256 mm matrix size, slice thickness = 1mm, no skip).

**Image Processing**

The gray matter volume analysis was conducted using the Statistical Parametric Mapping (SPM8) software (www.fil.ion.ucl.ac.uk/spm). Data was processed using the Voxel-Based Morphometry (VBM8) toolbox (www.neuro.uni-jena.de/vbm/) in SPM8. Details of these pipeline is described previously. Briefly, T1-weighted images were bias-corrected, tissue segmented (gray matter, white matter, cerebral spinal fluid), and registered into a standard space using both linear (12-parameter affine) and non-linear transforms. We used Template-O-Matic (TOM8) software (www.neuro.uni-jena.de/software/tom/) to create an age appropriate standard template to which normalization parameters were calculated for each subject. Data was visually inspected for artifacts and the homogeneity of variance within our
sample was assessed using VBM guided boxplots and covariance matrices (data not presented). Next, those images that passed inspection were smoothed using an 8 mm full-width-half-maximum Gaussian kernel.

Statistical Analysis
Demographic variables were compared between groups and subgroups to determine the need to include any regressor variables in our statistical models. Next, general linear models (GLMs) were created to compare HRO and HCO groups, was well as across PAHRO, UAHRO and HCO subgroups. Results were visualized using SPM8. We used a cluster threshold of 50 voxels to correct for voxel-based Type I errors, and Bonferroni correction was used across all thresholded clusters within each comparison to control for cluster-based Type I errors. The WFUpickatlas toolbox (http://fmri.wfubmc.edu/software/pickatlas) with AAL and TD atlases were used to label structures at the peak MNI coordinates 47-49.

Results
Demographics
Age, sex and IQ were comparable between groups (HRO and HCO) as well as subgroups (PAHRO, UAHRO and HCO) (Table 1). Eighteen of children from the HRO group met criteria for current or past, or were subthreshold for one or more psychiatric diagnoses: major depressive disorder (n=9), anxiety related disorders including phobias (n=11), ADHD (n=6), opposition defiant disorder (n=2), or post-traumatic stress disorder (n=1).
Gray Matter Volume Analysis

During the inspection of the homogeneity of covariance of our sample, it was determined that data from two participants (1 UAHRO, 1 PAHRO) was outside of 2 standard deviations of the mean covariance values for our sample. These subjects were excluded from further analyses.

Compared to HCO, the HRO group showed decreased volume several brain regions (Table 2, Figure 1a). These included the right inferior orbitofrontal ($p_{cor} < 0.001$), 2 regions of the left superior temporal ($p_{cor} = 0.002, 0.002$), bilateral middle temporal (L/R: $p_{cor} = 0.001, <0.001$), 2 regions of the left precentral ($p_{cor} < 0.001, 0.002$), 4 regions of the right middle frontal ($p_{cor} = 0.002, 0.003, 0.003, 0.006$) and the right lateral occipital cortices ($p_{cor} = 0.002$). We found no significant regions of increased volume in HRO compared to the HCO group.

When further subcategorizing the HRO group into PAHRO and UAHRO, we observed that both groups had several regions of decreased volume compared to the HCO, while differences between these two groups were minimal. Compared to HCO, the PAHRO group showed ten regions of decreased volume (Table 2, Figure 1b). These regions included the right inferior orbitofrontal ($p_{cor} < 0.001$), regions of the left pre- and post-central ($p_{cor} < 0.001, <0.001, 0.001$), the right superior and middle temporal ($p_{cor} = 0.002, 0.001$), as well as the left superior temporal cortices ($p_{cor} = 0.002$). Compared to the HCO group, the UAHRO group showed several regions of
decreased volume, particularly in the frontal lobe (Table 2, Figure 1c). Of particular interest, the right inferior orbitofrontal ($p_{cor} = 0.002$), right middle frontal ($p_{cor} < 0.001, 0.004, 0.002$), right superior frontal cortices ($p_{cor} = 0.001, 0.002, 0.003$) and one region of the left superior frontal gyrus ($p_{cor} = 0.002$). When comparing HRO subgroups, we found decreased volumes in bilateral lateral occipital regions ($p_{cor} < 0.001$) in PAHRO compared to UAHRO.

Discussion

Our study was the first to directly compare gray matter volumes in symptomatic and asymptomatic high-risk offspring. In doing so, our results (1) provided further support for the presence of gray matter volume deficits in HRO, and (2) confirmed that these deficits are present irrespective of the presence of symptoms in HRO. Compared to HCO, both HRO groups showed decreased gray matter volume in the right inferior orbitofrontal, right middle frontal, and left superior and bilateral middle temporal regions. When comparing across HRO groups, we did not find differences in gray matter volumes in any regions of interest, however, we did find reduced volume in lateral occipital regions in PAHRO. In this paper, we previously explained the critical role of the prefrontal cortex in modulating limbic response to internal and external emotion processing. The superior temporal gyrus is highly sophisticated structure, containing specialized structures including Wernicke’s Area, responsible for processing language and speech, as well as Heschl’s Area, which play a critical role in auditory processing, and lastly the Planum Temporale, responsible for multisensory integration including vision with audition $^{50-54}$. Deficits
in the superior temporal gyrus have been associated with the presence of psychotic symptoms including auditory hallucinations $^{55,56}$.

Adolescence is defined as a period of highly sophisticated cortical reorganization, through processes of myelination and synaptic pruning $^{57-61}$. Not all cortical structures follow the same developmental or temporal trajectories across the cortex $^{57-61}$. Gogtay and colleagues mapped the cortical development across subjects 4-21 years of age and observed cortical maturation followed this temporal sequence: (1) primary sensorimotor cortices mature first, along with frontal and occipital poles, (2) maturation follows a projection from parietal to frontal (back to front), where (3) the last to mature are the prefrontal and temporal cortices; both regions of high-order integration and function $^{57}$. Since our study observed reduced gray matter volumes in prefrontal and temporal regions, we might posit that high-risk offspring follow a premature developmental trajectory where maturation, including synaptic pruning, may be occurring in these regions before their typically developing peers $^{58,62}$. There is a need for future studies to investigate regional trajectories across healthy and high-risk populations longitudinally, to help map the emergence of deficits over time.

A limitation to our study is that it is cross-sectional in design. This limits our ability to infer developmental trajectories in relation to the onset of gray matter volume deficits over time. For this study we separated symptomatic and asymptomatic HRO without certainty of which offspring will go on to develop BD. Our groups were
defined based on previous research supporting the increased risk of developing BD in those offspring who present with childhood ADHD, anxiety and/or mood symptoms. Moreover, our sample is mildly underpowered to compare HRO subgroups. This would work to increase data variability and noise within our sample, however, our results remained significant after correcting for multiple comparisons, suggesting these findings are robust. Future research should be geared towards investigating gray matter volumes in high-risk offspring populations longitudinally, to further support the use of these deficits as a vulnerability marker for BD.
Tables and Figures

Table 1 – Demographic information

<table>
<thead>
<tr>
<th></th>
<th>HCO (n=20)</th>
<th>Total (n=31)</th>
<th>HRO PA (n=18)</th>
<th>UA (n=13)</th>
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<tr>
<td><strong>Age average (SD)</strong></td>
<td>13.3 (2.5)</td>
<td>13.4 (2.8)</td>
<td>13.8 (2.6)</td>
<td>12.5 (3.0)</td>
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<tr>
<td>**IQ average (SD) *</td>
<td>114.7 (12.5)</td>
<td>109.6 (16.7)</td>
<td>105.8 (19.6)</td>
<td>114.23 (9.5)</td>
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<tr>
<td><strong>Sex # (% female)</strong></td>
<td>9 (45)</td>
<td>13 (42)</td>
<td>8 (44)</td>
<td>5 (38)</td>
</tr>
</tbody>
</table>

* IQ was assessed using Wechsler's Abbreviated Scale of Intelligence
Age, IQ or Sex did not meet significance between groups (HRO or HCO) or between subgroups (PA or UA or HC).
Table 2 – Regional gray matter volume differences between groups

<table>
<thead>
<tr>
<th>X, Y, Z Coordinates</th>
<th>BA</th>
<th>P&lt;sub&gt;cor&lt;/sub&gt; Values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HRO&lt;HCO</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Inferior Orbitofrontal</td>
<td>48, 36, -11</td>
<td>47</td>
</tr>
<tr>
<td>Right Middle Temporal</td>
<td>50, -24, -6</td>
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<td>32</td>
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<tr>
<td>Left Precentral</td>
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<td></td>
<td>-54, -7, 1</td>
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</tr>
<tr>
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<td>36, 62, 0</td>
<td>10</td>
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<td></td>
<td>24, 57, 24</td>
<td>10</td>
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<tr>
<td>Right Lateral Occipital</td>
<td>45, -72, 19</td>
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<tr>
<td><strong>PAHRO&lt;HCO</strong></td>
<td></td>
<td></td>
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<tr>
<td>Right Inferior Orbitofrontal</td>
<td>48, 39, -11</td>
<td>47</td>
</tr>
<tr>
<td>Left Precentral</td>
<td>-44, -9, 61</td>
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<tr>
<td></td>
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<tr>
<td>Right Lateral Occipital</td>
<td>38, -69, 19</td>
<td>39</td>
</tr>
<tr>
<td><strong>PAHRO&gt;HCO</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Lateral Occipital</td>
<td>44, -81, -5</td>
<td>19</td>
</tr>
<tr>
<td><strong>UAHRO&lt;HCO</strong></td>
<td></td>
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<tr>
<td>Right Inferior Orbitofrontal</td>
<td>48, 36, -11</td>
<td>47</td>
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<tr>
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<td>30, 22, -14</td>
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<tr>
<td></td>
<td>32, 60, 6</td>
<td>10</td>
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<td></td>
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<tr>
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<td></td>
<td>28, 50, 33</td>
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<tr>
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<td>Left Precentral</td>
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<tr>
<td>Right Superior Parietal</td>
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<tr>
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<td>51, -24, -6</td>
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<td><strong>UAHRO&gt;PAHRO</strong></td>
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<td>Left Lateral Occipital</td>
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<tr>
<td>Right Lateral Occipital</td>
<td>57, -66, -21</td>
<td>20</td>
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Figure 1 - Displaying regional gray matter volume differences from the VBM analysis in SPM on both the age-specific template created using TOM as well as on a glass brain. A) The results of decreased gray matter volumes in the HRO group compared to HCO group. B) The results of decreased gray matter volumes in the PAHRO subgroup compared to HCO group. C) The results of the decreased gray matter volumes in the UAHRO subgroup compared to HCO group.
Acknowledgements
The authors would like to gratefully acknowledge the Brain and Behavior Research Foundation (formerly known as NARSAD) for their financial contribution to this study, the children and their families for participating and our clinical nurses, Helen Begin and Cindy D’Amico for conducting all study interviews.

Disclosures
RBS receives consulting and speaker support from BMS, Jansen. The remaining authors do not have any associations that might pose a conflict of interest in relation to this manuscript.

Author Contributions
G.B.H. and R.B.S. were responsible for the study design. L.C.H. was responsible for the collection, interpretation of results, and preparation of the manuscript. All authors contributed to the provided feedback, including edits and conceptual feedback, on the manuscript at all stages.

References


Chapter 4

Cortical Thickness in Symptomatic and Asymptomatic Bipolar Offspring

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5 Associate Professor, Department of Psychology, Neuroscience & Behaviour, McMaster University, Hamilton, Ontario, Canada
Abstract and Keywords

**Objectives:** While we understand that children of parents diagnosed with bipolar disorder are at greater risk for developing a variety of psychiatric disorders, the reasons remain unknown. Gray matter volume studies in high-risk offspring (HRO) have revealed decreased volumes of inferior frontal gyrus and increased volumes in striatal and subcortical regions, while other studies have found no significant regional differences. The present study aimed to investigate gray matter integrity in high-risk and healthy offspring using cortical thickness techniques.

**Methods:** Here we examined healthy control offspring (n=20) and high-risk bipolar offspring with (n=17) or without (n=13) the presence of psychiatric symptoms. All offspring underwent a magnetic resonance imaging scan, where T1 weighted images were collected and cortical thickness and age-cortical thickness correlations were compared.

**Results:** Compared to healthy offspring, HRO showed cortical thinning in superior and inferior temporal regions, supramarginal, and caudal and rostral middle frontal regions. When comparing HRO with and without psychiatric symptoms, we found cortical thinning in symptomatic offspring in the superior frontal and somatosensory related cortices. Age-thickness correlations showed a relatively consistent negative relationship in most regions in healthy offspring, while the reverse was true for the high-risk offspring. These regions included parahippocampal, lateral orbitofrontal, and inferior temporal regions.

**Conclusions:** Our study provides evidence of cortical thickness deficits among symptomatic and asymptomatic high-risk offspring during youth. Our study suggests some of these deficits develop only when associated with the onset of psychiatric symptoms and were found in key regions of emotion processing and regulation.

**Keywords**
bipolar disorder – bipolar offspring – cortical thickness – MRI – biomarkers
Introduction

Bipolar disorder (BD) is a highly debilitating illness affecting 1-3% of the population globally. Individuals diagnosed with BD are left with more disability-adjusted life years lost than any other major neurological or health condition including cancer. BD is highly heritable, with rates of approximately 0.8 in first-degree relatives. Offspring with a parent diagnosed with BD are at 10 times greater risk of developing BD, as well as 3-8 times more likely to develop other psychiatric disorders. Moreover, BD offspring that present with symptoms of depression, anxiety and/or ADHD at a young age appear to be at highest risk for developing BD. Studying high-risk offspring (HRO) populations can help elucidate alterations in neuronal circuitry and biological markers of vulnerability that may exist before the onset of BD.

Structural abnormalities in adult and pediatric BD have been reported in regions of the prefrontal-striatal-limbic circuit; a circuit consistently implicated in emotional processing and regulation, and is central to our understanding of the neuroanatomical model of BD. Structural abnormalities in first-degree relatives are less consistent and have been previously reviewed. Specifically, bipolar offspring have been observed to have decreased volume in the inferior frontal gyrus, and increased volume in the caudate, right amygdala, and left parahippocampal/hippocampal regions. Several studies also reported no significant differences in gray matter volumes. Inconsistencies in study findings may be attributed to differences in methodology, including difference in age,
whether high-risk offspring presented with symptoms, and/or whether parents were diagnosed with BD type I or type II. To our knowledge, only one study has reported cortical thickness differences in first-degree relatives, 16-25 years of age, of individuals diagnosed with BD. This study reported reduced parahippocampal and fusiform regions in both first-degree relatives who went on to develop depression and first-degree relatives who remained unaffected. Papmeyer et al. further observed differential reductions in the inferior frontal and precentral cortices as a function of group and time.

The relationship between structure and age can be complicated. Adolescence is a time of complex developmental and maturational changes. Previous studies in healthy youth have found that not all structures follow the same developmental trajectory: for example the superior temporal gyrus has shown a linear decrease in volume over time, while the volumes of the postcentral and prefrontal regions follow an inverted quadratic relation over time. Adolescence is a particularly vulnerable developmental stage, where the emergence of many psychiatric disorders occur. Comparing regional trajectories across healthy and at-risk populations may help to map the emergence of deficits over time.

Gray matter integrity can also be examined by investigating cortical thickness. Cortical thickness methods are thought to directly measure the number of cells within a microcolumn of the cortex, and may be more sensitive to detecting subtle changes within the cortex that are associated with being at-risk. To date, no
studies have investigated gray matter structural integrity in HRO using cortical thickness measures. It was the aim of this study: (1) to evaluate cortical thickness in HRO compared to healthy control offspring, and (2) to compare age-cortical thickness correlations between offspring to consider differences in regional developmental trajectories. We further aim to investigate symptomatic and asymptomatic HRO to elucidate structural abnormalities related to the development of psychiatric symptoms. Based on prior studies investigating gray matter volumes and cortical thickness, we hypothesized that HRO would demonstrate abnormalities in brain regions associated with emotional processing and regulation, including cortical thinning of the inferior frontal gyrus, anterior cingulate and parahippocampal regions.

Methods

This study was conducted in accordance with the Hamilton Integrated Research Ethics Board. Participants were recruited from inpatient and outpatient mental health services at St. Joseph’s Healthcare Hamilton, and Hamilton Health Services, as well as the Psychology Department at McMaster University and local advertisements throughout the greater Hamilton area, Ontario, Canada. Written parental consent and child assent were obtained.

Participants

Thirty high-risk bipolar offspring (HRO) and twenty age- and sex- matched healthy offspring (HCO) were recruited for this study. All participants were between 8-16
years of age. The HRO group was required to have at least one biological parent diagnosed with BD, which was confirmed during the study. It was not an exclusion factor for HR offspring to have a diagnosis or symptoms of depression, anxiety and/or ADHD. Healthy offspring and their first-degree relatives were required to be free of any psychiatric disorders. Other exclusion criteria for all participants included the presence of a pervasive developmental disorder, a substance use disorder, a neurological condition, intelligence quotient (IQ) less than 70, or the presence of any contraindications for an MRI scan.

*Psychological Assessments*

All participants underwent a structured diagnostic interview using the Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime (K-SADS-PL)\textsuperscript{52}, during which raters were blind of parental diagnosis. This assessment was used to further classify HRO as partially affected (PAHRO: the presence of psychiatric diagnoses or symptoms at present of lifetime) or unaffected (UAHRO: the absence of any psychiatric disorders or symptoms, past or present). One biological parent for each participant was clinically assessed using the Structured Clinical Interview for the DSM-IV (SCID)\textsuperscript{53} to confirm a diagnosis of BD (for the HRO group), or the absence of any psychiatric disorders (for the HCO group). Trained clinical nurses conducted all interviews and a board certified child psychiatrist (RBS) reviewed all diagnoses. IQ was assessed with the Wechsler Abbreviated Scale of Intelligence (WASI)\textsuperscript{54}.
Data Acquisition

Before undergoing an magnetic resonance imaging (MRI) scan, participants were introduced to a mock scanner to acquaint them to the sounds and procedures of the MR, and improve the quality of image collection by reducing movement during the scan \(^{55,56}\). Magnetic Resonance Images were collected at St. Joseph’s Healthcare Hamilton using a General Electric 3T whole-body short-bore scanner (Milwaukee, WI). High-resolution T1-weighted images were collected using a 3D spoiled gradient recall pulse sequence: repetition time = 10.8ms, echo time = 2ms, flip angle = 20, field of view = 240mm, 256 x 256 mm matrix size, slice thickness = 1mm, no skip.

Image Processing

Cortical thickness analysis was conducted using FreeSurfer 5.1.0 software (http://surfer.nmr.harvard.edu). This program uses a surface-based analytical approach described previously \(^{57-59}\). Briefly, this semi-automated process involves the normalization and correction of signal intensity, removal of extra-cerebral voxels also known as skull stripping, and the creation of triangular tessellated boundaries bordering the gray/white and pial surfaces. This meshwork was created through classification of voxels as white or gray matter, with those voxels containing both classified as boundary voxels and were used for the calculation and smoothing of surface tessellations. At this point, boundaries were visually inspected and manual edits were performed in the case of misclassified gray or white matter. Once data passed careful visual inspection, it was normalized to a spherical template, and projected back onto a standardized brain space, and smoothed using a 10mm full-
width-half-maximum Gaussian kernel. Cortical thickness was calculated at each vertex and defined as the shortest distance between gray/white matter and pial surfaces.

Statistical Analysis

Demographic variables were compared using R 3.1.3 (www.r-project.com). The appropriate statistical test was chosen to compare IQ, age and sex across two groups and across three subgroups. This information was used to determine the number of regressors to use in our statistical models. FreeSurfer group descriptor files were modeled to compare differences between groups (t-tests). Clusters were required to have a minimum size of 50 mm². General linear models (GLMs) were constructed to compare age-cortical thickness correlations between groups. Clusters from these models were further restricted to a minimum size of 100 mm². R software was further used visualize statistically significant GLMs. To reduce the risk of type I error, all results were adjusted for multiple comparisons using a Bonferroni correction for all clusters larger than 50 mm² across two hemispheres for each comparison. Here we defined significance as \( p_{\text{cor}} < 0.01 \), and marginal significance as \( p_{\text{cor}} < 0.05 \).

Results

Demographics

There were no significant differences in age, sex or IQ between HRO and HCO (see Table 1). Additionally, there were no significant differences in age, sex or IQ
between partially affected, unaffected HRO or HCO. The majority of partially affected HRO presented with symptoms of anxiety and depression (see Table 1). A scanner update did take place during the course of the study, we compared cortical thickness between those pre- and post- update and found no significant differences in group patterns of cortical thickness.

*Cortical thickness in HRO and HCO*

In the right hemisphere, HRO showed significant cortical thinning in the inferior temporal gyrus ($p_{\text{cor}} = 0.003$), and in the supramarginal region ($p_{\text{cor}} = 0.01$). In the left hemisphere, HRO showed four regions of cortical thinning including two regions of the superior temporal gyrus ($p_{\text{cor}} = 0.01, p_{\text{cor}} = 0.02$), caudal middle frontal ($p_{\text{cor}} = 0.04$), and rostral middle frontal ($p_{\text{cor}} = 0.03$). HRO showed one region of increased cortical thickness in the left fusiform ($p_{\text{cor}} = 0.03$). These results are displayed in Figure 1a and Table 2.

*Cortical thickness in PAHRO, UAHRO and HCO*

Here we compared partially affected, unaffected HRO and HCO. Compared to HCO, PAHRO showed cortical thinning in the left superior temporal ($p_{\text{cor}} = 0.005$), left precentral ($p_{\text{cor}} = 0.02$), right insular ($p_{\text{cor}} = 0.008$), right inferior temporal ($p_{\text{cor}} = 0.03$), right superior frontal ($p_{\text{cor}} = 0.03$) and right supramarginal ($p_{\text{cor}} = 0.02$) regions (see Figure 1b and Table 2). Compared to HCO, UAHRO showed significant cortical thinning in the right inferior and middle temporal regions ($p_{\text{cor}} = 0.004, 0.008$) (see Figure 1c and Table 2). As well, UAHRO showed cortical thinning in the
right supramarginal region \( (p_{cor} = 0.01) \) and increased thickness in right postcentral gyrus \( (p_{cor} = 0.02) \). Lastly, we compared PAHRO and UAHRO (see Figure 1d and Table 2). Compared to unaffected HRO, PAHRO showed cortical thinning in the right superior frontal \( (p_{cor} = 0.001) \), bilateral precentral \( (L/R: p_{cor} = 0.007/0.004) \) and postcentral \( (L/R: p_{cor} = 0.004/0.004) \). PAHRO also showed marginally significant cortical thinning in the left superior parietal cortex \( (p_{cor} = 0.03) \).

**Cortical thickness-age correlations in HRO and HCO**

Here we examined age-thickness correlations between HRO and HCO (see Table 3, Figure 2a and Supplementary Figure 1). In all but one region, we found age-thickness correlations to be negative in the HCO group, and positive in the HRO group. These regions included the left inferior temporal \( (p_{cor} = 0.02, 0.04) \), right parahippocampal \( (p_{cor} = 0.001) \), left lateral orbitofrontal \( (p_{cor} = 0.02) \), right pericalcarine \( (p_{cor} = 0.02) \), left fusiform \( (p_{cor} = 0.003) \) and right inferior parietal \( (p_{cor} = 0.002) \). In the right rostral middle frontal, we found the age-thickness correlation to be positive in the HCO group and negative in the HRO group \( (p_{cor} = 0.007) \).

**Cortical thickness-age correlations in PAHRO, UAHRO and HCO**

Compared to HCO, PAHRO showed four regions of difference in age-thickness correlations (see Table 3, Figure 2b, Supplementary Figure 2). In the left paracentral \( (p_{cor} = 0.006) \), left lateral orbitofrontal \( (p_{cor} = 0.01) \) and right inferior parietal \( (p_{cor} = 0.0004) \), age-thickness correlations were negative in HCO and positive in PAHRO. This relationship was reversed in the HRO group in the right rostral middle frontal
(p_{cor} = 0.001). Compared to HCO, UAHRO also showed several regional age-thickness correlation differences (see Table 3, Figure 2c, Supplementary Figure 3). All but the right precentral region (p_{cor} = 0.002) showed negative age-thickness correlations in HCO and positive correlations in the UAHRO. And lastly, PAHRO and UAHRO groups were compared (see Table 3, Figure 2d, Supplementary Figure 4). In all but the right precentral region (p_{cor} = 0.002) we found a positive age-thickness correlation in the UAHRO, while the PAHRO group showed a negative correlation in the same region.

**Discussion**

Emotional processing and regulatory deficits have been marked as the cornerstone of bipolar disorder. While the deficits in bipolar offspring are less understood, it is reasonable to expect that deficits would appear in the same circuitry. To our knowledge, this study is the first to investigate gray matter integrity in high-risk bipolar offspring during childhood and adolescence through the use of cortical thickness techniques. Our results suggest cortical thinning in HRO in supramarginal, superior and inferior temporal as well as middle frontal regions. Structural deficits were further examined by comparing high-risk bipolar offspring with or without psychiatric symptoms. This analysis was used to help determine which deficits may develop before or after the onset of symptoms. Compared to HCO, both UAHRO and PAHRO showed cortical thinning in the right inferior temporal and supramarginal regions. Additionally, PAHRO showed cortical thinning of the superior frontal and somatosensory related cortices compared to UAHRO, and thinning of the superior temporal and insula compared to HCO.
We further investigated age-thickness correlations to map regional trajectories in HR groups. Here we found a decrease in cortical thickness in most regions as age increased in HCO. This relationship has been noted previously and thought to be reflective of cortical maturation processes such as synaptic pruning or myelination\textsuperscript{44,47,62-67}. Alternatively, we found positive correlations between age and thickness in lateral orbitofrontal and inferior parietal regions in PAHRO, as well as inferior temporal, parahippocampal and several somatosensory-related cortices in the UAHRO group. These findings are in line with one other previous study reporting on cortical thickness differences in first-degree relatives at familial risk for BD\textsuperscript{41}. It is possible that HRO follow a different developmental trajectory resulting in altered maturation of key regions responsible for processing and regulation of emotion.

The prefrontal-striatal-limbic pathway has largely been implicated as the neurocircuitry underlying BD. Prefrontal regions such as the dorsolateral prefrontal and orbitofrontal cortices are thought to down-regulate subcortical responses to emotionally salient stimuli\textsuperscript{18}. This pathway is responsible for the voluntary mediation of emotional response, also known as emotion regulation\textsuperscript{18-20,68}. Alternatively, the processing of emotion can be considered automatic and requires the recruitment of several specialized regions to both perceive emotionally salient cues and to understand social context\textsuperscript{68,69}. Beyond the primary visual cortex, the fusiform and superior temporal regions are engaged to construct a spatial representation of facial features and movements\textsuperscript{70-72}. Lesions of the insula,
operculum and somatosensory related cortices have been associated with impairments in emotional face labeling\textsuperscript{68,73}. Finally, somatosensory related cortices are also responsible for representing goals, intentions and actions in response to emotional stimuli\textsuperscript{68,73}. Our results may suggest cortical thinning can be found in regions involved in emotion regulation and processing, and may further suggest deficits seen in PAHRO may be more related to emotion regulation, while UAHRO deficits may be more related to emotion processing.

This study is not without its limitations. Like other neuroimaging studies, our sample is underpowered to compare HRO subgroups. The major difficulty with a small sample size is an increase in data variability and/or noise resulting in a loss of significant results. Here we demonstrate regions of cortical thinning and differences in age-thickness correlations between HRO subgroups and HCO, suggesting these findings are robust. Secondly, this study is cross-sectional in design and therefore we can only speculate as to the relationship between structural thickness and emerging symptoms over time. Future studies should investigate at-risk offspring before, during and after the onset of symptoms to better understand the developmental trajectories of these regions.

In conclusion, this study provides evidence of structural deficits in the form of cortical thinning in children of parents diagnosed with BD. Our study suggests some of these deficits develop along with the onset of psychiatric symptoms. Furthermore, when comparing symptomatic and asymptomatic HRO, this study
provides evidence for deficits in regions that have been associated with emotion processing and regulation.
Tables and Figures

**Table 1 – Demographic information**

<table>
<thead>
<tr>
<th></th>
<th>Age average (SD)</th>
<th>IQ* average (SD)</th>
<th>Sex # (% female)</th>
</tr>
</thead>
<tbody>
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<td><strong>HCO</strong> (n=20)</td>
<td>13.3 (2.5)</td>
<td>114.7 (12.5)</td>
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<tr>
<td><strong>HRO</strong> (n=30)</td>
<td>13.4 (2.8)</td>
<td>108.6 (16.3)</td>
<td>13 (43)</td>
</tr>
<tr>
<td>PAHRO (n=17)</td>
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<td>104.4 (19.2)</td>
<td>8 (47)</td>
</tr>
<tr>
<td>UAHRO (n=13)</td>
<td>12.5 (3.0)</td>
<td>114.2 (9.5)</td>
<td>5 (38)</td>
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</table>

<table>
<thead>
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<th>HCO</th>
<th>HRO Partially Affected</th>
<th>HRO Unaffected</th>
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<tbody>
<tr>
<td>Depression</td>
<td>0</td>
<td>9</td>
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</tr>
<tr>
<td>Anxiety</td>
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<td>6</td>
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<tr>
<td>Other</td>
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<td>2</td>
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* IQ was assessed using Wechsler's Abbreviated Scale of Intelligence.
Age, IQ or Sex did not meet significance between high-risk offspring (HRO) or healthy control offspring (HCO) groups or between partially-affected HRO (PAHRO), unaffected HRO (UAHRO) or HCO subgroups.
Table 2 – Results of surface-based cortical thickness analysis compared across groups

<table>
<thead>
<tr>
<th>Size mm²</th>
<th>Peak Coordinates X, Y, Z</th>
<th>P&lt;sub&gt;cor&lt;/sub&gt; value</th>
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<tr>
<td><strong>HRO vs. HCO</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HRO&lt;HCO</td>
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<td></td>
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<tr>
<td>R Inferior Temporal</td>
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<tr>
<td>L Superior Temporal</td>
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<td>L Rostral Middle Frontal</td>
<td>53.6</td>
<td>-43, 26, 17</td>
</tr>
<tr>
<td><strong>HRO&gt;HCO</strong></td>
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<td></td>
</tr>
<tr>
<td>L Fusiform</td>
<td>156.2</td>
<td>-34, -58, -13</td>
</tr>
<tr>
<td><strong>PAHRO vs. HCO</strong></td>
<td></td>
<td></td>
</tr>
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<td></td>
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<td>53, -23, 38</td>
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<td><strong>UAHRO vs. HCO</strong></td>
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<td><strong>PAHRO vs. UAHRO</strong></td>
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<td>L Precentral</td>
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<td>-27, -23, 50</td>
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P<sub>cor</sub> ≤ 0.05 (*), 0.01 (**), 0.001 (***)

HCO= Healthy control offspring, HRO=High-risk offspring, PAHRO= Partially-affected high-risk offspring, UAHRO= Unaffected high-risk offspring
Table 3 – Results of age-cortical thickness correlations compared across HRO and HCO as well as between PAHRO, UAHRO and HCO

<table>
<thead>
<tr>
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<th>Size mm²</th>
<th>Peak Coordinates X, Y, Z</th>
<th>P&lt;sub&gt;cor&lt;/sub&gt; value</th>
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<tr>
<td><strong>HRO vs. HCO</strong></td>
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<td>335.2</td>
<td>-44, -2, -32</td>
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<td>212.7</td>
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<td><strong>UAHRO vs. HCO</strong></td>
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<td>L Postcentral</td>
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<td>-35, -25, 47</td>
<td>0.0073 **</td>
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</table>

P<sub>cor</sub> ≤ 0.05 (*), 0.01 (**), 0.001 (***)
HCO= Healthy control offspring, HRO=High-risk offspring, PAHRO= Partially-affected high-risk offspring, UAHRO= Unaffected high-risk offspring
Figure 1 – Depicting regional cortical thickness differences between (A) all high-risk offspring (HRO) and healthy control offspring (HCO), (B) partially affected HRO (PAHRO) and HCO, (C) unaffected HRO (UAHRO) and HCO, (D) PAHRO and UAHRO. Refer to Table 2 for regional details.
Figure 2 – Depicting regional differences in cortical thickness-age correlations between (A) all high-risk offspring (HRO) and healthy control offspring (HCO), (B) partially affected HRO (PAHRO) and HCO, (C) unaffected HRO (UAHRO) and HCO, (D) PAHRO and UAHRO. Refer to Table 3 for regional details.
Acknowledgements
The authors would like to gratefully acknowledge the Brain and Behavior Research Foundation (formerly known as NARSAD) for their financial contribution to this study, the children and their families for participating and our clinical nurses, Helen Begin and Cindy D’Amico for conducting all study interviews.

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Author Contributions
G.B.H. and R.B.S. were responsible for the study design. L.C.H. was responsible for the collection, interpretation of results, and preparation of the manuscript. All authors contributed to the provided feedback, including edits and conceptual feedback, on the manuscript at all stages.

References


Supplementary Figures

Supplementary Figure 1 – Graphical representations of the regional age-thickness correlations between high-risk offspring and healthy control offspring.
Supplementary Figure 2 - Graphical representations of the regional age-thickness correlations between partially affected high-risk offspring and healthy control offspring.
Supplementary Figure 3 - Graphical representations of the regional age-thickness correlations between unaffected high-risk offspring and healthy control offspring.
Supplementary Figure 4 - Graphical representations of the regional age-thickness correlations between partially affected high-risk offspring and unaffected high-risk offspring.
Chapter 5

Accuracy of Emotion Labeling in Children of Parents Diagnosed with Bipolar Disorder

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² Associate Professor, Department of Psychology, Neuroscience & Behaviour, McMaster University, Hamilton, Ontario, Canada
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Abstract and Keywords

Objective: Emotion labeling deficits have been posited as an endophenotype for bipolar disorder (BD) as they have been observed in both patients and their first-degree relatives. It remains unclear, however, whether these deficits exist in first-degree relatives secondary to the development of psychiatric symptoms or whether these deficits can be attributed to a general risk for psychopathology. To explore this, we investigated emotion processing in symptomatic and asymptomatic high-risk bipolar offspring and healthy children of healthy parents.

Methods: Symptomatic (n=18) and asymptomatic (n=12) high-risk bipolar offspring (HRO) and age- and sex-matched healthy offspring (HCO, n=20) performed an emotion labeling task. Total number of errors, emotion category and intensity of emotion error scores were compared between groups. Correlations between total error scores and symptom severity were also investigated.

Results: Compared to HCO, the HRO group made more errors in total on the adult face task ($p_{cor}=0.004$). The HRO group were also 2.5 times [90% CI: 1.2 – 5.1] more likely to make errors on sad faces and 3.4 times [90% CI: 1.0 – 11.3] more likely to make errors on angry faces compared to the HCO group. We observed no significant differences in error patterns between symptomatic and asymptomatic HRO, and no correlations between symptom severity and total number of errors.

Conclusions: This study provides further support for emotion labeling deficits to be a candidate endophenotype for BD. While emotion labeling deficits have been confirmed in HRO, our study suggests these deficits are not attributed to the presence of psychiatric symptoms.

Keywords
bipolar offspring – high-risk offspring – emotion labeling – endophenotype
Introduction

Bipolar disorder (BD) is characterized by cyclic changes in mood that can cause serious disturbances in daily living. These mood changes are thought to be the consequence of dysfunction in the fronto-striatal-limbic pathway. This pathway is involved in the processing of emotion, as well as the regulation of intrinsic and extrinsic emotion states. Functional neuroimaging studies have observed an increased activation of the amygdala and other limbic regions, and a decrease in activation of prefrontal regions in response to emotionally salient stimuli (as reviewed by). Behaviourally, adults with BD perform more poorly on facial emotion processing tasks compared to healthy controls. These deficits have also been well validated in pediatric BD populations independent of mood state, and have been investigated in first-degree relatives of patients diagnosed with BD. As such, emotion labeling deficits have been posited as a potential endophenotype for BD.

Children of parents diagnosed with BD are at much greater risk of developing BD, as well as a variety of other psychiatric disorders. For this reason, these children are considered high-risk offspring. Additionally, those offspring who develop childhood anxiety, ADHD or unipolar depression appear to be at the highest risk for developing a diagnosis of BD later in life. As such, many studies investigating emotion labeling deficits in high-risk offspring populations have recruited either a purely asymptomatic offspring sample, or a combination of symptomatic (often anxiety and/or ADHD) and asymptomatic offspring to avoid sampling an overly...
resilient population\textsuperscript{19-21}. In the later case, these offspring are often represented as a single group, making the contribution of symptoms to emotion labeling deficits unclear. To our knowledge, no studies have made it their focus to examine whether there are differences in the emotion labeling capabilities of high-risk offspring who present with or without symptoms.

The Diagnostic Analysis of Non-Verbal Accuracy (DANVA)\textsuperscript{35} task is a well validated, computerized, emotion labeling paradigm that has recently been highlighted as an accurate measure of social and emotional skills in youth\textsuperscript{36-39}. The task was designed to measure a child’s ability to accurately identify basic emotions (happiness, sadness, anger and fear) under more normative conditions\textsuperscript{35,36}. That is, unlike other standardized face labeling paradigms, such as those based on the Ekman faces\textsuperscript{40}, the DANVA includes information such as hair, clothing and background within each stimuli which would better represent social conditions\textsuperscript{36}. Error patterns on the DANVA have been shown to distinguish at-risk offspring from healthy controls based on increased total number of errors\textsuperscript{19,41}, as well as across childhood psychopathologies\textsuperscript{17,42}. More specifically, Cadesky and colleagues distinguished children diagnosed with conduct problems as being more likely to misinterpret emotions as angry compared to ADHD and healthy children\textsuperscript{42}. Guyer and colleagues reported increased emotion labeling errors in children diagnosed with BD compared to a variety of other childhood diagnoses including anxiety, depression, ADHD and conduct disorder\textsuperscript{17}. 
In the present study, we investigated emotion labeling deficits in high-risk offspring with and without psychiatric symptoms, using the DANVA assessment tool. Specifically, we examined error patterns related to total scores, emotion type and intensity of emotion expression in order to identify error patterns that may differentiate symptomatic and asymptomatic high-risk offspring. We predicted that (1) both high-risk offspring groups would make more errors than healthy offspring of healthy parents\textsuperscript{19,41}, and (2) that error scores may differentiate offspring based on the presence of psychiatric symptoms.

Methods

Participants

Subjects included high-risk bipolar offspring (HRO, \(n=30\)), and age- and sex-matched healthy offspring of healthy parents (HCO, \(n=20\)). All children were between 8-16 years of age. This study was approved by the Hamilton Integrated Research Ethics Board. Parents and their children gave written consent and assent, respectively. For this study, HRO were defined as having at least one biological parent diagnosed with BD (type I or II). These offspring were not excluded for having a diagnosis or meeting subthreshold criteria for psychiatric conditions including depression, anxiety and/or ADHD. This information was used to further separate the HRO group into partially affected/symptomatic (PAHRO, \(n=18\)) or unaffected/asymptomatic (UAHRO, \(n=12\)). HCO were defined as being free of any psychiatric symptoms, as well as no family history of any psychiatric illness in any first-degree relatives. Exclusion criteria for all participants included the presence of
any pervasive developmental disorders, autism spectrum disorder, schizophrenia, any current substance use disorder, any neurological condition, or an IQ less than 70.

**Psychological Assessments**

The Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime version (K-SADS-PL)\(^{43}\) was used to assess the presence of any major psychiatric disorders in all offspring. During this interview, raters were blind to parental diagnosis. The Structured Clinical Interview for the DSM-IV (SCID)\(^{44}\) was used to assess the presence of psychiatric disorders in one biological parent for each offspring. In the case of high-risk offspring, the biological parent diagnosed with BD was required to undergo this interview. Trained clinical nurses conducted all interviews and a board certified child psychiatrist (RBS) reviewed all diagnoses. To investigate how emotion labeling errors might correlate with psychiatric symptoms, we further assessed symptoms of anxiety, depression and ADHD in all participants using the Multidimensional Anxiety Scale (MASC)\(^{45}\), Child Depression Inventory (CDI)\(^{46}\), and ADHD subsection of the Conners Parent Rating Scale (CPRS)\(^{47}\), respectively. Age, sex, and IQ (assessed with the WASI)\(^{48}\) were also ascertained.

**Emotion face labeling task (DANVA)**

The child face and adult face subtests of the DANVA task were administered to all participants. The DANVA task has been described previously\(^ {36,37}\). Briefly, children were given the choice of happy, sad, angry or fearful labels, and were asked to pick
the emotion that best described what the person (child or adult) in the photo was feeling. Each subtest was comprised of 24 faces: 8 of each emotion type (4x8), and 12 of each intensity type: high or low (2x12). We compared total error scores, emotional categorical errors and differences in errors between high and low intensity faces between offspring groups.

Statistical Analysis

All statistics were performed using R 3.1.3 software (www.r-project.org). Statistical tests were selected to compare demographic and clinical variables between groups (HRO and HCO) as well as subgroups (PAHRO, UAHRO and HCO). This information was used to determine which demographic variables would be used as regression variables in our statistical models. Clinical variable scores including the MASC, CDI and CPRS were compared to total error scores on adult and child subtests. This was done to determine the correlation between error in emotion labeling and the level of anxiety, depression and/or ADHD symptom severity. Given the distribution of our error data, we used nonparametric statistical tests to compare the total error scores, error rates across emotional categories and emotional intensity category between offspring populations. Mann-Whitney U and Kruskal-Wallis statistical tests were used, and both tests were corrected for multiple comparisons using Bonferroni correction. This data is represented in Figure 1 using Plot software (http://plot2.micw.eu/). Lastly, we used the significant results above to define a priori emotion types to compare using odds ratios. For this analysis, we compared the odds of making any errors (yes/no) in any emotion type between HRO and HCO.
Results

Demographic and Clinical Information

A total of 50 offspring participated in the study (see Table 1). Age, sex or IQ did not differ significantly between groups (HRO and HCO) or subgroups (PAHRO, UAHRO, HCO). The K-SADS-PL interview revealed that 18 children from the HRO group met current or past criteria or were subthreshold for one or more psychiatric diagnoses: major depressive disorder (n=9), anxiety related disorders including phobias (n=11), ADHD (n=6), opposition defiant disorder (n=2), and post-traumatic stress disorder (n=1). Next, MASC, CDI and CPRS scores were compared across groups. While MASC scores did not differ, CDI and CPRS scores were found to be significantly different between HCO and PAHRO as well as PAHRO and UAHRO groups. In both cases UAHRO and HCO group scores were comparable.

Total Error Rates

Compared to HCO, the HRO group showed a significant increase in the total number of errors made on the adult faces subtest ($p_{cor}=0.004$) (see Table 2). Our data identified that on average HRO were 1.4 times more likely to make errors on the adult face task compared to HCO. Post hoc analysis revealed no significant differences between symptomatic and asymptomatic HRO ($p_{cor}=1.0$). There was also a trend for increased total error score on the child faces task in the HRO group ($p_{cor}=0.08$).
Emotion Error Rates

HRO and HCO groups showed significant differences in error rates on the child angry faces (p_{cor} = 0.02), adult sad faces (p_{cor} = 0.01), as well as a trend towards differences in error rates for adult angry faces (p_{cor} = 0.06) (see Table 2). When comparing HRO subcategories, we found significant increased in error rates during the child sad faces in PAHRO compared to UAHRO (p_{cor} = 0.03). These differences are further illustrated in Figure 1. Happy and fearful emotion categories revealed no significant differences between groups.

Intensity Error Rates

Compared to HCO, the HRO group showed increase difficulty in correctly labeling high intensity emotion during the child faces task (p_{cor} = 0.02), and low intensity emotion during the adult faces task (p_{cor} = 0.003). In both cases, PAHRO and UAHRO groups had comparable error scores. These differences are further illustrated in Figure 1.

Error ratios

Our comparison of emotion-type errors revealed significant differences in mean error rates of angry and sad emotion types between HRO and HCO groups. This observation guided our calculation of odds ratios for both angry and sad emotions between HRO and HCO. Compared to HCO, HRO were 2.5 times more likely to make errors in sad emotion labeling [90% CI: 1.2 – 5.1], and 3.4 times more likely to make errors in angry emotion labeling [90% CI: 1.0 – 11.3].
Symptom Severity and Total Error Scores

We observed no significant correlations between total errors in either child or adult subtests in any of our clinical measures (CDI $p_{cor} = 0.34, 0.40$, MASC $p_{cor} = 0.92, 0.94$, CPRS $p_{cor} = 0.18, 0.87$).

Discussion

This study contributes to our understanding of BD and vulnerability in two ways: (1) we were able to replicate the findings of Brotman and colleagues who identified emotion labeling deficits in HRO \(^{19}\), and (2) our study is the first to directly compare emotion labeling deficits in symptomatic and asymptomatic HRO. With the exception of sad type emotion errors, our study revealed no discernible differences in total error rates, emotion or intensity errors between HRO with or without symptoms. Together with previous studies, our results suggest emotion labeling deficits are concurrent with risk or vulnerability, and may precede the onset of any psychiatric symptoms including those diagnostic of BD.

Our results demonstrated differential error patterns between HRO and HCO for angry and sad emotions. This finding stands in contrast to some previous work. For example, Brotman and colleagues reported HRO require greater intensity of facial affect to accurately label all emotion types, not only angry and sad \(^{20}\). Alternately, in line with our findings, several studies have reported comparable emotion processing deficits in HRO and in youth diagnosed with BD \(^{19-21}\). One recent study
compared DANVA errors scores in children with pediatric BD and reported increased in both total error score and angry emotion error scores. Consequently, further research is needed to confirm whether emotion type errors exist and are a consistent finding in high-risk populations.

Emotional processing is complex, requiring the accurate detection of emotionally salient stimuli as well as monitoring and regulating the emotional response. Beyond the primary visual cortex, regions such as the superior temporal sulcus and fusiform gyrus are recruited to help discern more specialized visual information including facial features and facial movements. It has also been observed that lesions to the insula, somatosensory related cortices and operculum are associated with emotionally salient stimuli. During the processing of emotional faces, functional imaging studies have reported decreased activation of prefrontal regions, superior temporal, anterior cingulate, and increased activation of subcortical regions including the striatum, amygdala, and thalamus in adults with BD compared to healthy adults. Connectivity studies have reported decreased negative connectivity between the amygdala and the ventrolateral prefrontal cortex, between the amygdala and the dorsolateral prefrontal cortex, and between the amygdala and the anterior cingulate cortex. Functional imaging studies in pediatric BD populations confer with adult studies for decreased activation of the ventrolateral prefrontal cortex, and increased activation of the amygdala and striatum, as well as some evidence for reduced connectivity between the amygdala and the posterior cingulate cortex or the precuneus. To our
knowledge, very few studies have compared neural correlates of emotional processing in HRO populations \(^{21,23,24,65}\). These studies report hyperactivation of the amygdala \(^{21}\), decreased activation of the inferior frontal gyrus \(^{24}\), and decreased functional connectivity between the amygdala-ventrolateral prefrontal cortex \(^{23}\).

Mourao-Miranda and colleagues were able to use machine learning techniques to separate HRO from HCO from differential activation of the ventral prefrontal cortex and superior temporal cortex during an implicit emotional processing task \(^{65}\). There is mounting evidence to suggest emotion processing deficits related to functional neuronal deficits in the fronto-striato-limbic pathway, however, it is unclear how early these deficits appear.

Deficits in emotion processing have been discussed previously as a potential endophenotype for BD \(^{19,21}\). Our results further support this notion. For a marker to be an endophenotype for a psychiatric disorder, it must meet the following five criteria \(^{66}\). (1) *It must be associated with illness in the population.* It is well established that BD is associated with emotion processing deficits. Dysfunction of the fronto-striatal-limbic pathway has been proposed as the consensus model for BD, and has been associated with emotion processing deficits seen clinically \(^2\). (2) *It is not state dependent.* Emotion labeling deficits were shown to remain present irrespective of mood state in pediatric BD \(^{12-17}\). (3) *It must be heritable.* It remains unclear whether these emotion labeling deficits are directly inherited. BD is among one of the highest heritable psychiatric disorders, with rates of approximately 0.8 in first-degree relatives \(^{25,67-72}\). Dean and colleagues observed that this rate increased
when more than one parent is affected. However, future studies should work towards investigating emotion labeling deficits in a longitudinal offspring study where it can be determined whether those offspring who go on to develop BD first present with these deficits. Depending on inheritance patterns, it must be present in first-degree relatives and/or at higher rates than the general population. Here, our research further confirmed the presence of emotion processing deficits in children at familial risk for the disorder. Moreover, its presence was independent of the development of symptomatology.

Due to our cross-sectional design, this study is limited in its ability to represent the trajectory of symptomatic and asymptomatic HRO. Our group categories were based on previous research supporting the increased risk of bipolar offspring who have developed symptoms of anxiety, ADHD and depression. Moreover, this design did not allow us to test the elements of causality or heritability of emotion processing deficits by virtue of having a bipolar parent. Future research should be geared towards investigating these relationships longitudinally, using a larger sample size, to further support the utility of emotion processing deficits as an endophenotype for BD.
### Tables and Figures

#### Table 1 – Demographic and clinical information

<table>
<thead>
<tr>
<th>Demographic Information</th>
<th>HCO (n=20)</th>
<th>HRO Total (n=30)</th>
<th>PA (n=18)</th>
<th>UA (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in Years average (SD)</td>
<td>13.3 (2.5)</td>
<td>13.4 (2.8)</td>
<td>13.8 (2.6)</td>
<td>12.8 (3.0)</td>
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<tr>
<td></td>
<td>114.7</td>
<td>105.8 (19.6)</td>
<td>115.4 (8.8)</td>
<td></td>
</tr>
<tr>
<td>IQ average (SD)</td>
<td>12.5</td>
<td>109.6 (16.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex # (% female)</td>
<td>9 (45)</td>
<td>13 (43)</td>
<td>8 (44)</td>
<td>5 (42)</td>
</tr>
</tbody>
</table>

#### Clinical Scales

| MASC average (SD)        | 51.1 (10.4) | 52.8 (11.4) | 56.4 (11.3) | 47.3 (9.3) |
| CDI average (SD) **      | 43.0 (7.4)  | 49.6 (11.8) | 54.7 (12.0) | 42.0 (6.1) |
| CPRS average (SD) **     | 46.7 (3.9)  | 58.5 (14.0) | 64.6 (14.3) | 49.4 (7.2) |

<table>
<thead>
<tr>
<th>K-SADS-PL past, present or subthreshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression (including MDD, or a major depressive episode)</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>Anxiety (including GAD, or specific phobias)</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>ADHD</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

HCO=Healthy control offspring, HRO= High-risk offspring, PAHRO=Partially affected high-risk offspring, UAHRO=unaffected high-risk offspring.

IQ was assessed using Wechsler's Abbreviated Scale of Intelligence. All clinical scores are presented as T values that have been age and sex corrected. Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime (K-SADS-PL) was used to assess past, present and subthreshold for diagnoses. Age, IQ or Sex did not meet significance between groups (HRO or HCO) or between subgroups (PA or UA or HC).

**p<0.05 between HCO and PAHRO, and between PAHRO and UAHRO, but not between UAHRO and HCO.
Table 2 – DANVA task total error scores, distribution of errors with respect to emotion and intensity

<table>
<thead>
<tr>
<th></th>
<th>HCO</th>
<th>HRO</th>
<th>HRO</th>
<th>HRO</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>PA</td>
<td>UA</td>
<td>UA</td>
</tr>
<tr>
<td><strong>Total Error Score</strong> (out of 24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult Faces **</td>
<td>4.4 (1.8)</td>
<td>6.1 (2.3)</td>
<td>6.1 (2.5)</td>
<td>6.2 (2.1)</td>
</tr>
<tr>
<td>Child Faces</td>
<td>2.8 (1.3)</td>
<td>4.0 (2.4)</td>
<td>3.9 (2.8)</td>
<td>4.0 (1.8)</td>
</tr>
</tbody>
</table>

**Adult Faces**

|                  |        |        |        |        |
| Emotion (out of 8) |        |        |        |        |
| Happy            | 0.60 (0.8) | 0.70 (0.8) | 0.50 (0.6) | 1.0 (1.0) |
| Sad *            | 0.40 (0.6) | 1.2 (1.3) | 1.3 (1.4) | 1.1 (1.1) |
| Angry *          | 1.75 (1.0) | 2.5 (1.4) | 2.4 (1.2) | 2.6 (1.7) |
| Fearful          | 1.6 (1.2) | 1.7 (1.2) | 1.9 (1.4) | 1.5 (1.0) |

**Intensity (out of 12)**

|        |        |        |        |        |
| High   | 1.5 (1.0) | 2.1 (1.4) | 2.1 (1.5) | 2.2 (1.2) |
| Low ** | 2.9 (1.1) | 4.0 (1.4) | 4.0 (1.6) | 4.0 (1.1) |

**Child Faces**

|                  |        |        |        |        |
| Emotion (out of 8) |        |        |        |        |
| Happy            | 0.25 (0.6) | 0.4 (0.6) | 0.50 (0.6) | 0.25 (0.6) |
| Sad *            | 0.25 (0.6) | 0.4 (0.7) | 0.61 (0.8) | 0.08 (0.3) |
| Angry *          | 1.4 (1.1) | 2.3 (1.4) | 2.1 (1.3) | 2.6 (1.4) |
| Fearful          | 0.85 (0.6) | 0.9 (0.8) | 0.72 (0.8) | 1.1 (0.8) |

**Intensity (out of 12)**

|        |        |        |        |        |
| High * | 0.45 (0.6) | 1.1 (1.1) | 1.1 (1.2) | 1.2 (1.0) |
| Low    | 2.3 (1.1) | 2.8 (1.7) | 2.8 (2.0) | 2.8 (1.3) |

HCO=Healthy control offspring, HRO= High-risk offspring, PAHRO=Partially affected high-risk offspring, UAHRO=unaffected high-risk offspring. All scores are displayed as the average number of errors (standard deviation) for each group.

* p<sub>cor</sub> < 0.05 between any comparison
** p<sub>cor</sub> < 0.01 between any comparison
Figure 1 – Mean and standard error of the total error scores, sad and angry emotion error scores, and high and low intensity error scores for both child and adult subtests of the DANVA.
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Author Contributions
G.B.H. and R.B.S. were responsible for the study design. L.C.H. was responsible for the collection, interpretation of results, and preparation of the manuscript. All authors contributed to the provided feedback, including edits and conceptual feedback, on the manuscript at all stages.

References


Chapter 6

Emotion Conflict Monitoring
and Conflict Adaptation in Bipolar Offspring

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Abstract and Keywords

**Introduction:** The clinical symptoms in Bipolar Disorder (BD) are thought to arise from dysfunction of the fronto-striatal-limbic pathway. This pathway is responsible for emotional processing and regulation and it is unclear whether deficits in this pathway exist before the onset of BD. Here we investigate neural correlates of emotional processing and regulation associated with risk by virtue of having a parent diagnosed with BD.

**Methods:** Symptomatic and asymptomatic children of parents diagnosed with bipolar disorder (termed high-risk offspring (HRO)), as well as healthy children of healthy parents (HCO) were recruited for this study. All children underwent a clinical diagnostic interview followed by a functional MRI scan while performing a modified emotional Stroop task. Images were processed using SPM8 and emotion conflict monitoring and conflict adaptation conditions were investigated.

**Results:** A total of 27 HRO [Average Age=13.5(2.7) years, 44% female] and 18 age- and sex-matched HCO [Average Age= 13.2(2.5) yrs, 50% female] were included in this analysis. Compared to HCO, the HRO showed increased engagement of the right insula, two regions of the right inferior frontal gyrus, bilateral caudate, and left thalamus during the emotion conflict condition and increased engagement of the right hippocampus, two regions of the right lingual, right thalamus and right occipital during the conflict adaptation condition.

**Discussion:** Our results contribute to the growing literature suggesting functional emotional processing deficits in HRO populations. Specifically, our results suggest that HRO have increased engagement of subcortical areas during the presence of conflict, as well as a lack of recruitment of top-down modulatory cortical regions that are similar to those found in individuals diagnosed with BD.

**Keywords**
Bipolar disorder – high-risk offspring – emotion conflict – conflict adaptation - fMRI
Introduction

Bipolar disorder (BD) is a chronic, debilitating illness whose diagnosis has life-long implications. Major symptoms of BD are thought to arise from abnormal functioning in the neural systems responsible for emotion processing and regulation 1-5.

Advances in the fields of neuroscience and biological psychiatry have lead to the identification of key neural pathways, and a greater understanding of how alterations, however small, can have major consequences including the development of psychiatric symptoms. While our understanding of these emotion regulation pathways have become better defined, it is unclear which disturbances contribute to the vulnerability and/or development of BD.

Successful emotion regulation in healthy adults

During successful emotion regulation, the prefrontal cortex plays a critical role by modulating the response of limbic regions, including the amygdala 6,7. The prefrontal cortex house a variety of highly distinct regions being responsible for difference types of emotion processing. For successful processing of internal mood state, the orbitofrontal or ventromedial prefrontal cortices become active, whereas for the perception of external emotionally salient stimuli, the ventrolateral prefrontal cortex is recruited 1-5. Finally, for more cognitive decisions on emotionally salient stimuli, the dorsal prefrontal cortex is recruited 1-5. The perception of emotional stimuli also involves more specialized and integrative regions, including the fusiform and superior temporal gyrus, which construct a spatial representation of facial features and movements, respectively 8-11.
Impairments in emotional face labeling have also been associated with lesions of the insula, operculum and somatosensory related cortices. Altogether, this high sophisticated network requires the recruitment of several specialized regions to perceive emotionally salient cues, understand context, and regulate emotional response.

*Emotion processing studies in BD*

Functional neuroimaging studies in both child and adult populations diagnosed with BD have converged on findings of increased activation of the amygdala, and decreased activation of prefrontal regions in response to emotionally salient stimuli. Behaviourally, adults diagnosed with BD perform worse on emotion processing tasks compared to healthy controls. These deficits have also been validated in pediatric BD populations, and in first-degree relatives of patients diagnosed with BD. As such, emotion labeling deficits have been posited as a potential endophenotype for BD. We will review these findings next.

Functional neuroimaging studies in BD support decreased activation of the inferior frontal, anterior cingulate, and ventrolateral prefrontal cortices, and increased amygdala reactivity in response to a variety of emotional salient paradigms. Moreover, functional connectivity studies have identified reduced inverse connectivity between the amygdala and ventrolateral prefrontal cortex, and the amygdala and anterior cingulate in the BD compared to controls. These findings remain consistent across adult and child populations, with
one exception. Interestingly, in unmedicated, predominantly euthymic pediatric BD populations, most studies report of increased activity of the anterior cingulate in response to emotional stimuli 46-49, suggesting this region may play a differential role in the course of the disorder.

*Emotion processing in children of parents with BD*

BD affects 1-3 percent of the population, with an increased prevalence in first-degree relatives 50-59. The offspring of parents diagnosed with BD are at greater risk of developing BD as well as other mood, anxiety, and/or disruptive behavior disorders 54,60-65. In addition, those children who go on to develop BD tend to have an earlier age of onset, greater symptom severity and a poorer prognosis compared to non-inherited BD 62,63,66-70. For these reasons, these children have been termed high-risk offspring (HRO).

To our knowledge, few studies have investigated emotional processing in HRO populations. Olsavsky et al. also studied first-degree relatives with ADHD and/or anxiety symptoms and reported increased activation of the right amygdala during implicit emotional-labelling task compared to a healthy group 30. Ladouceur and colleagues found (1) increased activation of the ventrolateral prefrontal cortex during an emotional distracters working memory task in healthy HRO, and (2) decreased inverse functional connectivity between the ventrolateral prefrontal cortex and amygdala in the HRO group (similar to BD) 32. Others have focused on executive functioning in HRO. Kim and colleagues found increased activity in the
ventrolateral prefrontal cortex and caudate, during a cognitive flexibility task, in unaffected first-degree relatives compared to a HC group. Thermenos et al. found increased activation in the inferior frontal gyrus, insula and superior parietal cortex, during a working memory task, in first-degree relatives with mood symptoms compared to HC group. Roberts and colleagues reported a specific lack of recruitment of the inferior frontal gyrus in response to emotional go/no-go task in unaffected first-degree relatives. Finally, Whalley et al. were able to distinguish those HRO who went on to develop depression by an increased activation of bilateral insular cortices, during an executive function task, compared to a healthy group and those HRO who did not go on to develop depression. While there is evidence of both emotional processing and executive functioning deficits appear in HRO, at this time, the results are variable. These differences may be attributed to methodological differences including recruitment of a study population with or without symptoms, risk from first-degree relatives with BD type I or type II, and/or task specific activation. A better understanding of what contributed to the differences in these deficits may help to further our understanding of vulnerability factors and the core psychopathology underlying BD.

Altogether, these findings help emphasize the need to find consistent, highly replicable biological markers for BD. The aim of this study was to investigate neural correlates of risk in children of parents diagnosed with BD. To do so, we used an emotion conflict paradigm, developed by Etkin and colleagues, that allows for the investigation of both emotion processing and executive functioning. Briefly, this
modified emotional Stroop task allows for the disassociation of emotional conflict monitoring and emotional conflict adaption neural systems. In healthy participants, conflict monitoring results in preferential recruitment of the anterior cingulate, medial prefrontal and amygdala, where as in situations of conflict adaptation result in the recruitment of the dorsolateral prefrontal cortices, all of which have been implicated in BD. We compared emotional conflict monitoring and adaptation capabilities in HRO to those of healthy offspring. From previous research we expected to find abnormal recruitment of the anterior cingulate and increased activation of the medial prefrontal cortices.

**Methods**

This research protocol was approved by the Hamilton Integrated Research Ethics Board. Participants were recruited through local advertising and through referrals from the inpatient and outpatient clinics at St. Joseph’s Healthcare Hamilton and McMaster Children’s Hospital. After a detailed description of the study, informed consent and assent were obtained from parent and child, respectively.

**Participants**

All participants were between 8-16 years of age. Exclusion criteria included a diagnosis of a pervasive developmental disorder including autism, a substance use disorder, a diagnosis of obsessive compulsive disorder or schizophrenia, a neurological condition such as epilepsy, an intelligence quotient (IQ) of less than 70, history of head trauma, or the presence of any contraindications for an MRI scan.
For this study, high-risk offspring (HRO) were defined as having at least one biological parent diagnosed with BD. Healthy offspring (HCO) were required to be free of psychiatric disorders and have no family history of any psychiatric disorders within their first-degree relatives. The Structured Clinical Interview for DSM-IV (SCID) was used to confirm a diagnosis of BD (Type I or II) in HRO parents and to confirm the absence of psychiatric disorders in parents of the HCO group. The Kiddie Schedule for Affective Disorders Present and Lifetime (K-SADS-PL) diagnostic interview was used to assess past, present or subthreshold diagnoses in all participants. We allowed for a variety of diagnoses in HRO to ensure we did not recruit an entirely resilient population. Raters were blind to the parent diagnosis while conducting the child interviews and a board certified child psychiatrist reviewed all findings (RBS). In addition to age, sex, IQ was obtained using the Wechsler Abbreviated Scale for Intelligence (WASI).

**Experimental Task**

The emotion conflict paradigm, developed by Etkin and colleagues, was selected for this study to better investigate differences in emotion conflict monitoring and conflict resolution functioning in HRO. Details of this task have previously been described. Briefly, participants were asked to identify the facial expression (either happy or fearful) while ignoring an emotional word across the face (either happy or fear). At times the word and face match (congruent condition) and at others they did not (incongruent condition) (Figure 1A). Incongruent trials were considered a
situation of high conflict, resulting in longer reaction times than those of congruent trials (also known as the Stroop effect). Etkin et al., also proposed that the sequence in which these trials were presented can have behavioural effects. When an incongruent trial is immediately followed by another incongruent trial, there is an improved reaction time when compared to a congruent trial followed by an incongruent trial (known as conflict adaptation). This paradigm has since been used in a variety of clinical populations.

Happy and fearful faces were taken from the Ekman and Friesen dataset. Hair and background were occluded using an 18% grey oval cutout and, in red capital letters, the word ‘happy’ or ‘fear’ was written across each face. The paradigm consisted of 74 happy and 74 fearful trials; each face was presented for 1s, followed by an interstimulus interval between 3-5s, during which a fixation cross appeared. The presentation was balanced for equal number of congruent-congruent (cC), congruent-incongruent (cI), and incongruent-incongruent (iI) pairings. To avoid repetition and priming effects, stimuli were never presented in the same order. Participants are asked to respond as quickly and as accurately as possible. Stimuli were presented and behavioural responses and latencies were captured using E-prime software (www.pstnet.com).

Data Acquisition

All participants were introduced to a mock scanner prior to the MRI session to help them become familiar with the sights and sounds of the MR scanner. This has
been shown to improve image quality particularly for children at younger ages\textsuperscript{81,82}. A General Electric 3 Tesla whole-body short-bore scanner with 8 parallel receiver channels was used to acquire images (Milwaukee, WI). Functional images were collected using a T2* interleaved echo-planar imaging sequence: 29 axial slices, flip angle $60^\circ$, $TE = 40$ ms, $TR = 2000$ ms, $FOV = 24$ cm, matrix $64 \times 64$, slice thickness = 4 mm, no skip. High-resolution T1-weighted images were collected using the following parameters: 3D spoiled gradient (SPGR) pulse, IRP sequence, flip angle $20^\circ$, $TE = 2$ ms, $TR = 10.8$ ms, $TI = 400$ ms, $FOV = 24$ cm, matrix $256 \times 256$, slice thickness = 1 mm, no skip.

\textit{Image Processing}

The images were processed using a standard pipeline in SPM8 (www.fil.ion.ucl.ac.uk/spm/). Functional images were realigned, motion corrected, coregistered to their anatomical counterpart, normalized into a standard space, and smoothed with an 8mm Gaussian kernel. Motion graphs were visually inspected and a cutoff of $>5$mm for gradual movement and $>2$ mm rapid movement was used to flag any scans requiring further motion correction using Artifact Detection Tools (www.nitrc.org/projects/artifact_detect). This toolbox was used to detect and remove volumes containing motion outliers. Scans were excluded if greater than 5\% of the volumes contained motion outliers.

General linear models (GLMs) were modelled for each participant and included motion correction and outlier regressors. Performance of the task was used to build
individual protocol files so that only accurate responses were modelled. We used a cutoff of 60% total accuracy on the task to ensure the effects were not at random. As a result 5 participants were excluded. Contrasts were developed to test conflict monitoring/Stroop effect [(iI + cl) – (cC + iC)] and conflict adaptation [iI – cl].

Data Analysis and Statistics
All clinical and behavioural variables were compared using R 3.1.3 software (www.r-project.com). At the group level, the main effects of group as well as between-group effects were compared using one-sample and two-sample t-tests, respectively. Age and task performance measures were included as covariates in the model to account for individual variability. Activation maps were gray matter masked, and thresholded for a minimum cluster size of 20 voxels. Finally, to identify the structures at peak coordinates, the Harvard-Oxford cortical and subcortical atlases were used.

Results

Demographic and clinical information
A total of 51 participants completed the study. Of these, 5 participants were removed due to low accuracy on the emotional conflict task, and 1 participant was removed due to excessive movement. There were no significant differences in sex, age or IQ between groups (Table 1). Seventeen children from the HRO group met criteria for one or more psychiatric disorders: Anxiety related disorders including general anxiety disorder and specific phobias (n=10), depressive related disorders
including a major depressive episode or MDD (n=8), ADHD (n=6), Oppositional Defiant Disorder (n=2), and past Post Traumatic Stress Disorder (n=1). There were no significant differences in demographic variables between symptomatic and asymptomatic HRO.

Behavioural results

There were no significant group differences on the task in accuracy (HRO: accuracy (SD)= 83.5 (8.3)%, HCO: accuracy (SD)= 84.8 (7.1)% or reaction time (HRO: average (SD)=794(175) ms, HCO: average (SD)=786(135) ms). Both groups showed significant delays in reaction time when responding to incongruent stimuli when compared to the reaction times of congruent stimuli (HRO: p=0.0001, HCO: t=-7.9, df=17, p<0.0001). This effect did not differ between groups. We compared the reaction times between cI and iI trial pairings as a behavioural measure of conflict adaptation, however, these results were not significant (HRO: p=0.55, HCO: p=0.34). In this comparison, symptomatic HRO showed less conflict adaptation than asymptomatic HRO (p=0.02)(Figure 1B).

Imaging results

Here we tested the main effects and group differences in conflict monitoring and conflict adaptation paradigm conditions.
a. Conflict monitoring

There was no main effect of this condition in the HCO group ($p_{uncor} > 0.01$), while the HRO group showed bilateral activation of the inferior frontal gyrus (R: MNI coordinates: 48, 12, 15, peak $p_{uncor} = 0.00001$, L: MNI coordinates: -46, -20, 10, peak $p_{uncor} = 0.00005$). Compared to the HRO group, the HCO group showed increased activation of the right planum temporale (MNI coordinates: 46, -20, 10, peak $p_{uncor} = 0.001$). Compared to the HCO group, the HRO group showed increased activation of the right insula, two regions of the right inferior frontal gyrus, bilateral caudate, and left thalamus (Table 2, Figure 2).

b. Conflict Adaptation

The main effects of conflict adaptation in the HCO were activation in the left paracingulate (MNI coordinates: -4, 24, 54, peak $p_{uncor} = 0.002$), right dorsolateral prefrontal (MNI coordinates: 46, 34, 30, peak $p_{uncor} = 0.004$), right inferior frontal (MNI coordinates: 52, 26, 28, peak $p_{uncor} = 0.008$), left superior frontal (MNI coordinates: -24, 12, 52, peak $p_{uncor} = 0.004$) and left occipital cortices (MNI coordinates: -44, -62, 44 peak $p_{uncor} = 0.004$). In contrast, the main effect of the HRO was activation of the right hippocampus (MNI coordinates: 36, -31, -7, peak $p_{uncor} = 0.0001$) and bilateral lingual cortices (L: MNI coordinates: -12, -54, -10, peak $p_{uncor} = 0.0001$, R: MNI coordinates: 13, -52, -8, peak $p_{uncor} = 0.0001$). Compared to the HCO group, the HRO group showed increased activation in the right hippocampus, two regions of the right lingual, right thalamus and right occipital (Table 2, Figure 2). Additionally, compared to the HRO group, the HCO group showed increased activity
in the left paracingulate, two regions of the inferior frontal cortex, and bilateral dorsolateral prefrontal cortices (Table 2, Figure 2).

**Discussion**

To the best of our knowledge, our study is the first to compare neural correlates of emotion conflict monitoring and adaptation in HRO. This study resulted in three major findings: (1) symptomatic HRO performed worse than asymptomatic HRO and HCO when comparing the differences in reaction time during the conflict adaptation. Although the average change in reaction times were faster for the adaptation condition for both HCO and asymptomatic HRO, these behavioural effects were not significant. Similarly, age did not explain this variability. It is possible that this adaptation is not fully developed during youth and that the significant differences in reaction times of symptomatic and asymptomatic HRO, this early on are depicting a difference in development of this emotion conflict adaptation network. (2) During conflict monitoring, the HRO group showed increased activation of the inferior frontal, insula, thalamus and caudate regions. (3) During conflict adaptation, the HRO group showed increased activation of subcortical regions, including the hippocampus, thalamus and lingual gyrus, whereas, the HCO group showed increased engagement of the paracingulate/medial prefrontal, inferior frontal and dorsolateral prefrontal regions.

Our results in HCO deviated from the expected results found in healthy adults. Specifically, we did not find recruitment of the anterior cingulate cortex, a key
region in the integration of cognitive and affective stimuli. Behaviourally, children under 7 years of age have been observed to have much longer reaction times and be much less accurate in response to visual-spatial conflict tasks. One study, conducted by Adleman and colleagues, asked participants between 7-22 years of age to perform a colour-word Stroop task while undergoing an fMRI scan. Their results showed that while the young adults (18-22 years of age) recruited regions of the anterior cingulated, inferior and middle frontal regions when performing the task, their child counterparts (7-11 years of age) showed reduced to minimal activation of these regions. We speculate these neural networks are not solidified early in life but rather follow a developmental course.

Moreover, during conflict monitoring the main effect of our HRO group was increased bilateral activation of the inferior frontal gyrus. This finding is in line with previous functional imaging studies in HRO, and in some studies of children with BD. Meanwhile, this activation is reversed in adults with BD, suggesting this functional correlate plays an important role in the development and progression of BD. It is possible that increased activation of the inferior frontal gyrus is a compensatory mechanism early on, and that this mechanism becomes extinguished later in life through the development of a BD. Future studies should aim to investigate the development of these neural networks longitudinally.

A limitation of our study was the increased signal to noise ratio that is inheritant when working with younger populations. We tried to address this issue in a variety
of ways, including an introductory visit with our mock scanner. Similarly, the imaging data from each participant was uniquely modelled based on individual accuracy, and trials involving motion outliers were used as additional regressors when creating our GLMs. Despite our best efforts, our results did not survive correction for multiple comparisons. For this reason, we did not investigate differences in neural correlates during the emotional conflict task between symptomatic and asymptomatic offspring.

In summary, our study highlighted potential aberrant functional differences in HRO populations that are in line with previous studies in high-risk and pediatric BD populations. Our findings suggest a possible increase in engagement of subcortical areas (including the hippocampus, thalamus and caudate) during the presence of conflict, as well as a lack of recruitment of top-down modulatory cortical regions (including the medial prefrontal, inferior frontal and dorsolateral prefrontal cortices) in the HRO group compared to our HCO group. We posit that these differences in function do not allow for the same conflict monitoring and adaption, as compared to a healthy control population, and that these changes may be reflective of an altered developmental trajectory. Future studies are required to better understand how these circuits develop and what factors contribute to altered psychopathology.
Tables and Figures

Table 1 – Demographic information

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<th>HCO (n=18)</th>
<th>HRO (n=27)</th>
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<td><strong>Age in years</strong> average (SD)</td>
<td>13.2 (2.5)</td>
<td>13.5 (2.7)</td>
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<tr>
<td><strong>IQ</strong> average (SD)</td>
<td>115.4 (12.9)</td>
<td>110.4 (16.4)</td>
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<tr>
<td><strong>Sex # of females (%)</strong></td>
<td>9 (50)</td>
<td>12 (44)</td>
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HCO = healthy control offspring, HRO = High-risk offspring, SD = standard deviation
Table 2 – Between-group functional activation results

<table>
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<th>X, Y, Z Coordinates</th>
<th>( P_{\text{uncor}} ) Values</th>
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<tr>
<td><strong>Conflict Monitoring [cC+iC]-[cI+iI]</strong></td>
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<td><strong>HRO&gt;HCO</strong></td>
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<td>Right Insula</td>
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<td>Left Thalamus</td>
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<td><strong>Conflict Adaptation [iI-cI]</strong></td>
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<tr>
<td><strong>HRO&gt;HCO</strong></td>
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<td>Right Hippocampus</td>
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<td>Right Occipital</td>
<td>36, -68, 14</td>
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<td><strong>HCO&gt;HRO</strong></td>
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<tr>
<td>Left Occipital</td>
<td>-44, -62, 44</td>
<td>0.001</td>
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</table>

cC = congruent-congruent trials, cI= congruent-incongruent trials, HCO= Healthy control offspring, HRO= High-risk offspring, iC= incongruent-congruent trials, il=incongruent-incongruent trials
Figure 1 – (A) Displaying congruent and incongruent conditions of the task as well as expected behavioural results during emotion conflict monitoring and adaption. Adapted from Fig. 1. (B) Showing the mean and standard error of reaction time differences (in milliseconds) of conflict adaptation (il-cl) and stroop effect (cC+iC)-(cl+il) conditions between healthy control offspring and asymptomatic and symptomatic high-risk offspring.
Figure 2 – Functional activation maps comparing high-risk offspring and healthy control offspring. (A) Displaying regions of increased activity in high-risk offspring compared to healthy control offspring during conflict monitoring (emotional Stroop). (B) Displaying regions of increased activity in healthy control offspring compared to high-risk offspring during conflict adaptation. (C) Displaying regions of increased activity in high-risk offspring compared to healthy control offspring during conflict adaptation.
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Author Contributions
G.B.H. and R.B.S. were responsible for the study design. L.C.H. was responsible for the collection, interpretation of results, and preparation of the manuscript. All authors contributed to the provided feedback, including edits and conceptual feedback, on the manuscript at all stages.

References


Successful social cognition results from appropriate perception, inference, and judgement of interpersonal and environmental cues. In order to be successful, one must develop a set of skills that allows for the accurate identification of social cues, a bank of experience that allows for the inference of an appropriate response, cognitive flexibility to go between attentional demands, and an ability to monitor and regulate ones own intrinsic emotional state. There are number of contributing factors that determine the success of this cognitive domain, some of which will be presented in this chapter as they relate to psychosocial impairments in Bipolar Disorder (BD).

Individuals with BD have been observed to have impairments in social cognition. Those with BD have reported having trouble initiating and maintaining interpersonal relationships, as well as having difficulties coping in social situations. Social cognitive impairments have also been observed to worsen with increased illness burden and increased number of mood episodes. An integral part of successful psychosocial functioning is the perception of social cues, and/or in its most basic form, the accurate identification of emotion. Most consistently, adults with BD have shown deficits in emotion face labelling irrespective of mood state. Similarly, adults with BD show difficulties placing their thoughts outside of their own context. This concept is known as theory of mind, and individuals with BD have been observed to score poorly on these tasks. Children diagnosed with BD
have also known deficits in social cognition, suggesting these impairment do not
develop as a consequence of illness burden, but rather exist at the onset or perhaps
precede the onset of the disorder. Children diagnosed with BD have been observed
to perform worse on emotional face labelling tasks, as compared to demographically
matched healthy controls 17-23. Similarly, one study observed that these children
perform more poorly on theory of mind tasks 24. Some studies have suggested these
deficits are associated with altered parent-child interactions, including a decrease in
maternal warmth 25-28. Studies that investigate the children of parents diagnosed
with BD give insight into whether psychosocial impairments develop before or after
the onset of psychiatric symptoms. These studies have varied on their observed
impairments 29,30. Reichart and colleagues noted that psychosocial impairments
during late adolescence and included decreases in adaptive functioning, and family
functioning on the Child Behaviour Checklist (CBCL) and Young Adult Self-Report 29.
Meanwhile, Bella and colleagues found that bipolar offspring of all ages showed mild
psychosocial impairments across a variety of measures including the CBCL,
Children’s Global Assessment Scale and the Adolescent Longitudinal Interval
Follow-up Evaluation 30. These studies provide evidence for these impairments to
precede the onset of psychopathology, and that these impairment gradually worsen
over time 29,30. While social cognitive impairments have been confirmed in both at-
risk and affected populations, the underlying cause for these deficits remain
unambiguous.
It is becoming increasingly apparent that structural and functional neuronal deficits in brain networks that mediate emotion processing and emotion regulation underlie bipolar illness. These networks are highly sophisticated and involve the recruitment of many specialized brain regions. Most notably, ventral prefrontal regions, including the ventrolateral prefrontal (inferior frontal) and ventromedial prefrontal (orbital frontal) cortices, are responsible for the modulation of the amygdala in response to external and internal emotional cues, respectively 31-34. Amygdala hyperactivation coupled with reduced ventral prefrontal activity are the most commonly reported functional imaging findings, and are thought to lead to the emotional extremes in BD 35-46. Moreover, deficits in executive functioning, including working memory, have been observed and validated in individuals with BD, involving more dorsal regions of the prefrontal (caudal and rostral middle frontal) cortex 31,33,47,48. These two systems, dorsal and ventral, are integrated by the anterior cingulate cortex, which is also thought to monitor discordant information 49-54.

In this thesis, we reviewed all available literature published by November 2014 on cortical thickness in individuals with BD. Here we found a convergence in findings on decreased thickness of the left anterior cingulate, left superior temporal, and widespread thinning across prefrontal regions including the medial, dorsolateral, ventrolateral and orbitofrontal cortices. As cortical thickness is direct measure gray matter integrity, these results suggest that BD is not only related to regional functioning or the communication between brain regions, but is also associated with aberrant structural changes at the level of the cortical cell columns.
By examining behavioural, structural and functional correlates in high-risk populations, we may further elucidate the neurobiological underpinnings related to risk for the disorder and in turn understand mechanisms of onset and progression of illness. In this thesis, we presented gray matter volume and cortical thickness analyses to investigate the gray matter integrity in children of parents diagnosed with bipolar disorder. Our results suggest both decreases in gray matter volume as well as cortical thinning in some of these key emotion processing and regulatory regions. Compared to healthy children of healthy parents, high-risk offspring showed reduced volume in the right inferior orbitofrontal, right middle frontal, bilateral superior temporal and bilateral middle temporal regions. However, when comparing high-risk offspring with or without symptoms, these regional volumes were comparable, suggesting these deficits are a function of risk is not associated with the development of symptoms. Similarly, compared to healthy children of healthy parents, high-risk offspring showed reduced gray matter thickness in the right caudal and right rostral middle frontal, left superior temporal, right inferior temporal and right supramarginal regions. Comparatively, in those high-risk offspring who presented with symptoms showed reduced thickness in the right superior frontal, left superior parietal and bilateral pre- and post-central cortices. While the results between gray matter volume and cortical thickness analysis among high-risk offspring and healthy control offspring where comparable, we observed differences in the results between these techniques when comparing symptomatic and asymptomatic high-risk offspring. We speculate that cortical thickness techniques are more spatially conserved and may be better at detecting
more subtle gray matter changes. It is possible that cortical thickness measures would be better at detecting these minor changes earlier on.

In this thesis, we also investigated emotion processing among high-risk offspring by comparing the behavioural effects during an emotion labelling task. Here our results contribute to our understanding of BD and vulnerability in two ways: (1) we were able to replicate the findings of Brotman and colleagues who identified emotion labelling deficits in high-risk offspring \(^{17}\), and (2) to the best of our knowledge, our study was the first to directly compare emotion labelling deficits in symptomatic and asymptomatic HRO. Compared to healthy control offspring, high-risk offspring had significantly higher total error scores when labelling adult faces. These high-risk offspring were also 2.5 times [90\% CI: 1.2 – 5.1] more likely to make errors on sad faces and 3.4 times [90\% CI: 1.0 – 11.3] more likely to make errors on angry faces compared to the healthy control offspring group. We also observed that these deficits were not associated with symptom presence or severity, again suggesting that these deficits are a function of risk and are not associated with the development of symptoms.

Lastly, we also compared the functional neurocircuitry underlying emotion conflict monitoring and conflict adaptation in high-risk offspring. Here, differential engagement of higher-order cognitive regions occur as a function of viewing discordant emotional salient information. In healthy adults, during the viewing of discordant emotional information (a situation of high conflict), there is preferential engagement of an emotion conflict monitoring neural network involving medial and dorsolateral prefrontal cortical regions. Meanwhile, during sequential repeated
exposures to discordant emotional information (a situation of low conflict), there is adaptation occurs, whereby there is preferential engagement of the anterior cingulate cortex. Here, we observed that compared to healthy control offspring, high-risk offspring showed increased engagement of the emotion conflict monitoring network, including the right inferior frontal cortex. We also observed increased activation of the right insula, left thalamus and bilateral caudate during this condition. During the conflict adaptation condition, in healthy control offspring, we observed increased recruitment of the left inferior frontal, left paracingulate/medial prefrontal and bilateral dorsolateral prefrontal cortices compared to high-risk offspring. Meanwhile, high-risk showed increased activation of right subcortical regions, including the hippocampus and thalamus. Our results in healthy control offspring deviated from the expected results found in healthy adults, which may reflect that these neural networks are not established early in development but rather follow a developmental course. Moreover, high-risk offspring at the same developmental stage appear to have more difficulty engaging this system. Future studies should aim to investigate the development of these neural networks longitudinally.

The contribution of our findings in relation to previous work is illustrated in Table 1. When investigating previous working in high-risk offspring with respect to the presence of symptoms, we see minimal difference in the observed deficits. In an entirely asymptomatic high-risk offspring population, Ladouceur and colleagues reported increased parahippocampal/hippocampal volume, which has not been reported in symptomatic high-risk offspring. In contrast, both groups showed
reduced volumes in middle frontal and superior temporal, a finding that carries over to BD populations. To our knowledge, only one other study has investigated cortical thickness deficits in high-risk offspring populations. This study suggested that those high-risk offspring who went on to develop MDD after a two year follow-up showed increased cortical thickness in the inferior frontal and reduced thickness in the precentral gyrus. In contrast, when comparing age-thickness correlations in our study population, we found positive correlations in the pars orbitalis and pars triangularis in asymptomatic high-risk offspring and negative correlations in these regions in symptomatic high-risk offspring. We found the opposite relation to be true for the precentral gyrus. We expect that our results may differ due to study design: (1) our study was cross-sectional, limiting our ability to validate individual differences in cortical thickness over time, and (2) we included of a variety of psychiatric disorders including depression, anxiety and ADHD disorders as compared to their focus on MDD outcomes in youth. Future research should focus on examining these trajectories longitudinally across a variety of psychiatric outcomes. Finally, functional studies in asymptomatic high-risk offspring have observed similar findings to those in individuals with BD, with the exception of increased ventrolateral prefrontal cortical activation in high-risk offspring. Few studies have investigated functional neural correlates in an entirely symptomatic population, however, these results are comparable. These findings again suggest functional neural deficits are a product of risk and exist irrespective of the development of symptoms.
While studying social cognition in bipolar offspring may be among the best avenues for discovering biological markers for BD, researchers should take caution in designing and interpreting the results of such studies. One such example would be to include more rigorous criteria for measuring behaviours. One difficulty with working with children and adolescents is the differentiation between typical and atypical behavioural associated with some developmental periods (namely, irritability, mood swings, defiance and/or emotional outbursts during adolescence). Moreover, studies have shown that some parental reports on child behaviours are influenced by parental mood state. Another such example would be accurately modelling the role of development. It would be inappropriate to expect the same social cognitive demands across this age group as we understand this skill set develops gradually. Studying at-risk youth across this critical time period may give insight into the precise time points of these psychosocial developmental milestones, as well as further our understanding of what traumas occur and at what stage these trajectories become altered. For example, it is apparent that some psychosocial impairments including emotional face labelling are consistent across mood state, have been observed to appear before the onset of a disorder, and gradually worse with increase illness burden. Further exploration of this may help to determine biological markers of social cognitive impairment that predict the onset of a disorder, and others that may predict illness progress or burden.
This study has its strengths and limitations. One strength of our study was the inclusion of a thorough diagnostic interview (the Kiddie Schedule for Affective Disorders Present and Lifetime and the Structured Clinical Interview for DSM-IV for children and adults, respectively) conducted by certified and experienced clinical nurses. Behavioural questionnaires of mood and temperament were chosen based on their validity and were considered supplementary to the interviews. Another strength was the inclusion of both unaffected and partially affected bipolar offspring populations, that were separated based on increased risk for developing BD, as defined by the literature. In doing so we were able to directly compare neural correlates of risk and resilience as they related to the presence and absence of psychiatric symptoms. One limitation to our study was its cross-sectional design. With this, we were restricted in our ability in refer developmental trajectories, and the validity of these markers over time. Futures studies should aim to investigate these offspring populations longitudinally to more accurately map biological markers of risk to those who do go on to develop BD. A final strength of our study was the use of multiple imaging modalities. These techniques allowed for the investigation of structural and functional neural correlates. And lastly, a final limitation of our study was a small sample size when comparing subsets of high-risk offspring. It was particularly challenging to recruit unaffected high-risk bipolar offspring. We posit a number of factors that contributed to this difficulty: (1) lack of centralized research study recruitment in Hamilton, Ontario, (2) lack of interest of healthy children of bipolar parents to be assessed, (3) eligibility of high-risk offspring was also dependent on the sex- and age- matching of other high-risk
offspring participants, and (4) participants needed to be eligible for an MRI scan
(common contraindications included mild anxiety toward small spaces, and braces).

In summary, regardless of the presence of a psychiatric illness, being at-risk,
by virtue of having a parent diagnosed with BD, was enough to produce deficits in
social cognition. Our results provide (1) further support for the existence of
behavioural, structural and functional correlates of risk in high-risk offspring. These
findings are in line with both previous high-risk offspring findings as well as with
expected trajectories for child and adult BD literature. (2) They provide support that
these deficits are a function of inherent risk and, with the exception of cortical
thickness, exist irrespective of the presence of symptoms in high-risk offspring.
### Table 1 – A review of research findings together with previous studies

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<th>Combined UA/PAHRO</th>
<th>PAHRO</th>
<th>BD</th>
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<tr>
<td>GMV:</td>
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<td></td>
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<td></td>
<td>- ↑ parahippocampus/hippocampus, trend for ↑ amygdala, OFG 55</td>
<td>- ↑ IFG 65, Amygdala 66</td>
<td>- ↓ OFG, superior temporal, middle temporal, precentral, superior parietal, precentral, postcentral (Chapter 3)</td>
<td>- ↓ ACC 49,69-72</td>
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<td>- ↓ middle frontal, middle temporal, caudate 55</td>
<td>- ↓ OFG, middle temporal, precentral, superior temporal, middle frontal, occipital (Chapter 3)</td>
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<td>- ↑ subcortical (thalamus, BG, accumbens, amygdala) 70,73,74</td>
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<tr>
<td></td>
<td>- ↑ caudate 60</td>
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<td>- ↓ dorsal or ventral PFC 32,72-75</td>
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<td>CT:</td>
<td></td>
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<td>(↓ density 79)</td>
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<tr>
<td></td>
<td>- ↓ inferior temporal, supramarginal, middle temporal, ↑ postcentral (Chapter 4)</td>
<td>CT:</td>
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<td></td>
<td>CT:</td>
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<td></td>
<td>- ↓ parahippocampal, fusiform 56</td>
<td>- ↑ inferior frontal, ↓ precentral 56</td>
<td>CT:</td>
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</tr>
<tr>
<td></td>
<td>- ↓ inferior temporal, superior temporal, supramarginal, caudal middle frontal, rostral middle frontal, ↑ fusiform (Chapter 4)</td>
<td>- ↓ inferior temporal, superior temporal, superior frontal, supramarginal (Chapter 4)</td>
<td></td>
<td>- all available papers reporting on CT in BD was reviewed in Chapter 2</td>
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<td>Function</td>
<td>Activation:</td>
<td>Activation:</td>
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<td></td>
<td>- ↑ vlPFC 80,81</td>
<td>- ↑ insula, IFG, caudate, thalamus, hippocampus, lingual (Chapter 6)</td>
<td>- ↑ amygdala 85</td>
<td>- ↑ ACC in children 36,37,87,88</td>
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<td>- ↓ OFG 82</td>
<td>- ↑ OFC, insula, superior parietal 86</td>
<td>- ↑ amygdala 35-44</td>
<td>- ↓ ACC in adults 41,46,89,90</td>
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<td>- ↑ caudate 81</td>
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<td>- ↓ amygdala vlPFC 35-38,41-43,45,46</td>
<td>- ↑ amygdala 35-44</td>
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<td>Connectivity:</td>
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<td>- ↑ vlPFC-superior parietal 83</td>
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<td>- ↓ amygdala- PCC/precuneus 91</td>
<td>- ↓ amygdala- fusiform 91</td>
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<td>- ↓ amygdala- ACC, vlPFC-caudate, ACC-supplementary motor cortex 83</td>
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<td>- ↓ amygdala- vlPFC 44,46</td>
<td>- ↓ amygdala- ACC 89</td>
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<td>Machine learning:</td>
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<td>- ↓ amygdala- dlPFC 44</td>
<td>- ↓ amygdala- dlPFC 44</td>
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<td>- medial PFC and OFG 84</td>
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</table>

Green depicts research included in this thesis, black depicts previous work. ACC = Anterior cingulated cortex, BD = Bipolar disorder, CT = Cortical thickness, dlPFC = dorsolateral prefrontal cortex, GMV = Gray matter volumes, HCO = Healthy control offspring, HRO = High-risk offspring, IFG = Inferior frontal gyrus, NSD = no significant differences, OFG = Orbitofrontal gyrus, PAHRO = Partially affected high-risk offspring, PFC = Prefrontal cortex, UAHRO = Unaffected high-risk offspring, vlPFC = ventrolateral prefrontal cortex.
References


