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Hannah Goldstein April 3, 2013

Behavioral and Cortisol Reactivity in Preschool Aged Children at High-Risk for Bipolar Disorder

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Abstract

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By Hannah Goldstein

This study examined behavioral and cortisol reactivity in preschool offspring of mothers with Bipolar Disorder (BD). Maternal diagnosis was considered as a moderating factor to explain the association between behavior and cortisol. Offspring of parents with BD are at high risk for developing the disorder and other negative outcomes, but research can illuminate prodromal signs and symptoms that will aid in diagnosis, treatment, and intervention. In a case control study, 161 preschool-aged children whose mothers either had BD, Major Depressive Disorder (MDD) or no Axis I diagnoses were exposed to a stressor task designed to evoke anger, sadness, and protest. Behavior was measured with a standardized assessment. Baseline and post-stressor cortisol levels were measured through salivary samples. Offspring of mothers with BD showed significantly higher levels of protest than the other groups, but no other significant group differences were found. Additionally, maternal diagnosis was not a significant moderator of the relationship between behavioral reactivity and cortisol. The results are consistent with recent literature on high-risk offspring and pediatric BD that emphasize externalizing behaviors as a core characteristic and concern. As there is little research on children at risk for BD and no identified investigations on preschoolers, this study is an important contribution to the literature examining the onset of signs and symptoms in high-risk children.

Keywords: behavioral reactivity, cortisol reactivity

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Behavioral and Cortisol Reactivity in Preschoolers at High-Risk for Bipolar Disorder

As the prevalence of adult and pediatric Bipolar Disorder (BD) increases, so does interest in the nature of the disorder. In just ten years, the number of adult diagnoses has risen from 1.6% (Kessler et al., 1994) to 2.6% of the United States population, with 82.9% of cases considered "severe" (Kessler, Chiu, Demler, & Walters, 2005). The prevalence of pediatric BD has increased as well, with some research reporting that diagnoses have doubled among outpatients to about six percent (Youngstrom, Youngstrom & Starr, 2005) and quadrupled among inpatients, to represent about 34.1% of psychiatrically-related discharges (Blader & Carlson, 2007). Due to the rising numbers and concerns about the population's increased risk for additional negative outcomes, such as suicide (Dalton, Cate-Carter, Mundo Parikh, & Kennedy, 2003) and comorbid disorders (McElroy et al., 2001; see review in Henin et al., 2005), BD is an important focus of prevention and treatment research.

BD research assesses populations who are affected and those at high risk to understand the etiology, development, and core features of the disorder (Hodgins, Faucher, Zarac, & Ellenbogen, 2002). With significant past attention paid to the presentation and clarification of core symptoms, a more recent body of literature has emerged to investigate the genetic and environmental risk factors that influence development of the disorder. Research on development looks for patterns and abnormalities in high-risk populations, often focusing on offspring of parents with the disorder. Offspring are 2.5 times more likely to develop BD and 4 times more likely to develop an affective disorder, such as Major Depressive Disorder (MDD) or Anxiety Disorder (Lapalme, Hodgins, & LaRoche, 1997). They are also at increased risk for behavior problems, resulting in high rates of Attention Deficit Disorder (ADHD), Conduct Disorder (CD), and Oppositional Defiant Disorder (ODD; Chang, Steiner, Dienes, Adleman, & Ketter, 2003).

Therefore, abnormalities in offspring may signify prodromal signs and symptoms that could be addressed in preventions and treatments to improve outcomes.

A Prospective Approach

While it is impossible to completely predict psychopathology, patterns in developmental pathways illuminate risk factors and warning signs. Comparisons of normal and abnormal populations at all ages reveal the onset and development of biological, psychological, and environmental abnormalities that may contribute to development of the disorder (Mash & Wolfe, 2013).

There are two methods for studying development: retrospective reports on diagnosed populations and prospective studies on high-risk ones. Prospective designs are considered the more optimal scientific approach as they best protect against the recall and confirmation biases of retrospective accounts (Mash & Wolfe, 2013). As noted above, the most commonly studied high-risk group for heritable disorders, such as BD, is offspring whose parent's psychopathology increase their genetic and environmental risk for the disorder and other negative outcomes (Hasler, Drevets, Gould, Gottesman, & Manji, 2006). The current study uses a prospective high-risk research design that follows mothers from pregnancy to assess child outcomes during a critical period of development, the preschool age.

Because the average age of onset for BD is in late adolescence or early adulthood (Duffy, Alda, Hajek, Sherry, & Grof, 2010), a high-risk study on preschoolers would not focus on the outcome of BD itself, but on characteristics that suggest inherited risk or preceding symptoms that will lead to later diagnoses. Specifically, we will compare offspring of mothers with BD to offspring of mothers with MDD or no Axis I Disorders to assess if those at high risk for BD

demonstrate the increased emotion, behavior, and cortisol regulation deficits that relate to the disorder.

Endophenotypes of BD

To determine which characteristics are relevant and therefore worth researching, it is important to consider previously found markers of future risk, called endophenotypes. Serving as an observable intermediary between genotype and phenotype, endophenotypes allow researchers to determine genetic vulnerabilities from overt symptoms (Glahn, Thompson, & Blangero, 2007). The most consistently reported neuroimaging endophenotypes in individuals with and at high-risk for BD are in the brain regions responsible for the assessment of emotionality and behavioral regulation. There is little research on high-risk populations specifically, but one study found hyperactivation of the amygdala while processing fearful faces (Olsavsky et al. 2012). Similarly, a number of studies on diagnosed individuals suggested that the decreased amygdala volume found early in development of the disorder might precede diagnosis (for a review, see Hajek, Carrey, & Alda, 2005). As the amygdala is important in assigning emotional significance to stimuli and mediating autonomic responses, the identified abnormalities indicate that individuals with and at risk for BD are more likely to interpret stimuli as fearful and respond with inappropriate displays of emotion and behavior (Davis & Whalen, 2001).

There is also evidence of endophenotypes for high-risk populations in brain regions that control inhibition, autonomic responses to emotional experiences, and regulation of socially appropriate behavior, namely the gyrus, cortices, and striatum (see review in Hajek, et al., 2005). One study found decreased activation of the left inferior frontal gyrus when high-risk individuals tried to control responses to fearful facial stimuli. (Roberts et al., 2012). As there are similar findings in family members, first-episode patients, and children and adolescents with BD,

abnormalities in the gyrus likely precede diagnosis (see review in Hajek et al., 2005). Additionally, there is evidence of increased gray matter volume in the left hemisphere of the brain, decreased gray matter volume in the right, bilateral loss in the cingulated cortices, and changes in subgenual prefrontal cortex and striatum among offspring, first episode patients, and adolescents and children with BD, which suggest a similar early onset. The increased risk of abnormalities in size and function of brain regions that control stimulus interpretation and response have led us to predict that high-risk individuals for BD will demonstrate a propensity to interpret negative stimuli as "fearful" through maladaptive behavioral and emotional displays. We aim to assess their ability to regulate autonomic responses and social appropriateness through measures of anger, sadness, protest, and cortisol as they indicate behavioral and stress reactivity.

Environmental risks associated with maternal BD

Environmental factors must also be considered in the development of BD, as the disorder is not solely attributable to genetics (Chang, Blasey, Ketter, & Steiner, 2001). For children, caregivers are the main source of social interaction and behavioral modeling, and therefore the most influential environmental risk factor (Denham, 2007). Preschoolers first learn how to cope, articulate needs, formulate socially appropriate responses, and identify the causes of their emotion under their parent's guidance and support. Parents with BD, however, are less likely to provide such support (Chang et al., 2001). Their symptoms and poor emotion, behavior, and stress regulation typically increase their own stress and stress for those around them. Their "psychotic, dysfunctional, neglectful, or absent" parenting styles negatively impact the organization and cohesion of their family, resulting in offspring that are more likely to show anger and less likely to be prosocial, academically successful, and socially accepted.

There are a number of models that relate parental personality traits and psychopathology with offspring behavior, which support the direction of the current research. Based on their own longitudinal study, Ostiguy, Ellenbogen, and Hodgens (2004) found that parents with BD and high levels of neuroticism, or the propensity toward feelings of stress (Costa & McCrae, 1992), were less supportive, had more stressful homes, and that their offspring showed increased externalizing and internalizing behavior problems (Ellenbogen & Hodgins, 2004) that predicted interpersonal deficits in adulthood (Ostiguy, Ellenbogen, & Hodgins, 2012). The authors postulate that the offspring's genetic risk for both the disorder and neuroticism is exacerbated by the parent's stress dysregulation, which manifests in poor modeling, unstable relationships, and stressful home environments. Thus, the parent increases the offspring's vulnerability to stress, and through environmental influences, decreases their ability to cope with it.

Behavioral reactivity and BD

The following study aims to contribute to the developing literature on behavioral patterns in high-risk youth and expects emotion and behavior dysregulation as they are common characteristics in adult BD, pediatric BD, and frequently comorbid disorders (Leibenluft & Rich, 2008). While criteria for adult BD focus on mood dysregulation, recent clinical observations have postulated that behavioral dysregulation may be a more developmentally appropriate description for children showing signs of the disorder. Incidence of euphoric mania before adolescence is rare, with an average age of onset at 17-19 years (Duffy, et al., 2010). In addition, children seem to display more chronic symptoms, more rapid mood cycles, and irritability instead of euphoric mania, leading to proposed changes to diagnostic criteria for children (Leibenluft & Rich, 2008). Research on high-risk populations have found similar concerns of general "behavior problems" in older offspring of parents with BD that relate to later diagnoses

(Carlson & Weintraub, 1993; Hirshfeld-Becker, Biederman, Henin, Faraone, Dowd, De Petrillo, Markowitz, & Rosenbaum, 2006; Ellenbogen & Hodgins, 2004) In light of recent concerns it is important to study behavior problems in young children to identify the onset, specific behaviors, and whether the proposed criteria capture core symptoms in children. It is important to note that the current study does not seek to diagnose children, with BD. Instead, it aims to examine behavioral deficits and their association with familial risk.

The current study is focusing on externalizing behaviors, rather than internalizing ones, as they relate more closely to core components of childhood BD and are stronger predictors of later interpersonal functioning (Ostiguy, Ellenbogen, & Hodgins, 2012). We tested behavioral reactivity in response to stressors, as individuals with BD are more likely to interpret stimuli as stressful and struggle with adaptive responses. In consideration of the developmental stage and genetic and environmental risk, we expect offspring of mothers with BD to show increased behavioral reactivity, operationalized by anger, sadness, and protest in response to stressors. Behavioral reactivity captures an inability to regulate negative emotions and suppress socially inappropriate responses to stress.

Cortisol and BD

The following study also aims to assess offspring's vulnerability to stress through the endocronological measure of cortisol. Cortisol influences emotion, behavior, psychology and neurobiology, making it instrumental in stress management (see review in Stansbury & Gunnar, 1994). Unfortunately, dysregulation is common in many psychopathological disorders, including BD, so offspring are, once again, at high genetic and environmental risk for abnormalities.

Cortisol is regulated by the Hypothalamic-Pituitary Adrenocortical (HPA) axis, one of two stress systems controlled by the central nervous system (see review in Gunnar & Quevedo,

2007). The HPA axis is activated by the presentation of stressful stimuli, when the amygdala, the brain region associated with fear, releases hormones that stimulate the hypothalamus. The hypothalamus releases corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP), which activate the anterior pituitary gland to release adrenocorticotropic hormone (ACTH). ACTH then acts on the cortex to release cortisol and epinephrine. Cortisol alters gene expression (de Kloet, Vreugdenhil, Oitzl, & Joels, 1998) and works as a feedback inhibitor to prepare the body for action, regulate other stress-sensitive systems, and formulate behaviors and emotional displays (see review in Stansbury & Gunnar, 1994).

While increases in cortisol often accompany negative emotionality in times of stress, there are inconsistencies across situations and individuals that suggest the role of moderating factors (see review in Stansbury & Gunnar, 1994). Researchers are still trying to understand the complex interaction between cortisol and internalizing and externalizing behaviors, but the most promising theory hypothesizes that tolerance of frustration and perception of control significantly predict cortisol abnormalities. According to the theory, elevations in cortisol occur when individuals are easily distressed by limitations and feeling out of control. Therefore, individuals who have increased salience to stressful stimuli and do not learn necessary coping mechanisms, e.g. children of parents with BD, may be more likely to show increased cortisol responsivity. Based on the emotion and stress regulation deficits of the disorder and evidence of elevations in adults with BD (Schmider, Lammers, Gotthardt, Dettling, Holsboer, Heuser, 1995) and adolescent offspring at high risk (Ellenbogen, Hodgins, & Walker, 2004), the following study expects cortisol abnormalities to onset during the preschool period, a critical time of development.

The current study predicts that cortisol abnormalities will appear from a young age because research has identified a sensitive period early in development during which caregiver treatment and behavior impact the efficiency of stress related neurobiological mechanisms in offspring (Gunnar & Donzella, 2002). As previously noted, children learn through modeling and guidance (Ostiguy et al., 2012). Unfortunately, children do not learn to alleviate stress or convey emotion when their mothers model ineffective coping strategies and are too overwhelmed by their owns tress to provide adequate support in response to their children's displays (Gunnar & Donzella, 2002). As a result, the child experiences frequent and prolonged exposure to stress and cortisol, which negatively impact neurobiological structures, emotion, and behavior regulation.

Maternal stress has particularly profound effects when accompanied by psychopathological disorders. One study that compared offspring of mothers with MDD and offspring of mothers with no diagnoses reported that children exposed to maternal stress in preschool and infancy children showed significantly higher levels of cortisol in preschool and more symptoms of psychopathology in first grade, with the strongest effects in the MDD group (Essex, Klein, Cho, & Kalin, 2002). Given the genetic and environmental risk factors, it is not surprising that maternal psychopathology would exacerbate offspring problems.

The current study hopes to fill a gap in the literature on cortisol reactivity in offspring at high risk for BD. There is limited research on the onset of cortisol abnormalities in relation to BD, with more attention paid to offspring at risk for MDD. One study on adolescent offspring at risk for BD did find higher basal cortisol levels, which indicate that abnormalities may precede diagnosis, and therefore be relevant to our sample (Ellenbogen, et al., 2004). Cortisol is of particular concern as it's negative impact on emotion and behavior regulation may increase the

likelihood of negative outcomes, including psychopathology. Early detection, however, could allow for intervention that would stop and possibly even reverse neurobiological changes.

Relationship between Behavioral Reactivity and Cortisol as Moderated by Mother's Diagnosis

As previously mentioned, the relationship between behavioral and cortisol reactivity is unclear, so the following study hopes to contribute to the literature by exploring maternal diagnosis as a moderator. As frequent and prolonged elevation of cortisol may negatively impact development, it is important to understand why, in certain circumstances, children who show similarly negative behaviors show differences in cortisol reactivity. One study by Nachmias et al. (1996) suggested the importance of maternal support, which is why maternal psychopathology may be important. Their study compared children's reactions to stressors in the presence and absence of their mothers, finding that, while both securely and insecurely attached children responded to fearful stimuli with behavioral inhibition, only insecurely attached children showed elevations in cortisol. As a result, they predict that secure relationships provide children with the support and learned coping skills that decrease the perceived magnitude of stressors, thus allowing children to adaptively regulate both behavior and cortisol. The inconsistent and unsupportive parenting styles associated with the symptoms of BD, however, increase the likelihood of insecure attachment. Therefore, the current study expects that, as it affects parenting style and the child-caregiver relationship, maternal psychopathology will moderate the relationship between behavioral and cortisol reactivity.

The Current Study

The current study adds to the literature of prodromal signs and symptoms for BD by assessing behavioral and cortisol reactivity among a young, high-risk population. The study explores the strength of the relationship between cortisol and behavior in the population,

considering maternal diagnosis as a moderator. The extant body of literature on offspring of parents with BD focuses primarily on adolescents, and the current study is one of the first to study preschoolers. The two control groups, offspring of mothers with MDD and offspring of mothers with no Axis I diagnoses, allow us to compare patterns and risks between different affective disorders and with a lower-risk sample. It is hoped that this study will increase our understanding of the development of BD and potentially inform successful treatment and intervention strategies.

Clarification of Central Aims

Specifically, this study tests the following hypotheses:

Hypothesis one: offspring of parents with BD will have higher rates of behavioral reactivity, measured by anger, sadness, and protest, when compared to the controls, offspring of mothers with MDD and offspring of mothers with no Axis I diagnosis.

Hypothesis two: offspring of mothers with BD will have elevated cortisol reactivity when compared to the controls.

Exploratory hypothesis: the relationship between cortisol and behavioral reactivity will be moderated by maternal disorder.

Method

Participants

The sample included 161 children (86 females, 75 males) and their mothers. Children were eligible to participate if they were between ages two and a half and five and a half years and their mothers had a primary diagnosis of Bipolar Disorder (BD), Major Depressive Disorder (MDD), or did not have an Axis I diagnosis. Children were ineligible if they had major congenital illnesses that involved medical intervention or major cognitive delays that impaired

their ability to comprehend testing materials. Additionally, six participants were excluded because their fathers had BD, to ensure a focus on maternal diagnoses, and to reduce confounds in terms of biological or environmental risk.

Mothers were recruited through the Emory Women's Mental Health Program (WMHP) and community mailings. Mothers were contacted via phone, email, or mailings and were asked to participate in a laboratory study with their preschool aged child. Mothers from the WMHP had been followed from pregnancy in previous research, whereas mothers from the community participated in this study for the first time during the preschool follow-up.

Children ranged in age from 29 to 66 months (about 2.5 to 5.5 years), with an average of 45.5 months (about 4 years). The majority of mothers were Caucasian (81.4%), with 10.6% African American, 4.3% Hispanic, 3.1% Asian, and 0.6% Biracial. 61.3% of children studied in a structured learning environment. Mothers ranged in age form 22 to 48 years, with an average of 37.07 years. 82.6% of mothers were married or living with someone as if married. The majority of mothers were highly educated, with 39.1% completing graduate or professional school, and 97.5% receiving more than a high school education or GED. The majority of families had more than one child in the home (75.8%).

Procedure

The mothers and children participated in a laboratory visit that lasted approximately two and a half hours. The visit was scheduled in the morning to ensure the child's maximum alertness and compliance. Upon arrival all mothers received a full description of the study, had an opportunity to ask questions, and were notified that they could withdraw data at any time. Mothers then provided written, informed consent for themselves and their children. During the visit, researchers reviewed the mother's psychopathological and family history through a semi-

structured interview. Children participated in a stress-inducing laboratory task designed to evoke and assess behavioral reactivity. Additionally, children's baseline and post-stress cortisol levels were assessed with two salivary samples, one immediately upon arrival and the other fifteen to twenty minutes after the stressor task.

Assessment of Behavioral Reactivity, The child participated in a videotaped stressor task. The task is part of the Laboratory Temperamental Assessment Battery (Lab-TAB), a standardized assessment of emotion and behavior regulation designed to evoke anger and sadness in response to realistic situations (Goldsmith, Reilly, Lemery, Longley, & Prescott, 1995). The task used was called "Impossibly Perfect Green Circles." The research assistant told the child to draw the "perfect green circle." After each attempt, the researcher critiqued the circle and asked the child to draw another. After the second attempt the researcher hung an example on the wall and said, "The last two kids that were here drew these circles and they are perfect. I need you to draw a perfect circle. The other kids thought this was easy," During the three minutes the researcher repeated the phrase "draw the perfect green circle" three times. At the end of three minutes the researcher ended the task by saying, "That circle looks really good! Circles are hard to draw. Let's go show your mom what a great job you did!"

Children's behavioral reactions to the Green Circles Task were coded offline (via video recordings) using a microcoding system that was used in previous research (Goldsmith, et al., 1995). Coders were blind to the parent's diagnosis, demonstrated reliability before coding, and met biweekly to discuss discrepancies, which were settled by the senior coder. The task was divided into 10-second epochs during which coders rated facial, bodily, and vocal indicators of emotion. Facial expressions of anger and sadness were assessed using the System for Identifying Affect Expression by Holistic Judgment (AFFEX), which allows researchers to code emotional

expressions based on universally recognized facial muscle patterns (Camras, Malatesta, & Izard, 1991). In addition, bodily anger, bodily sadness, indirect protest, and direct protest were also coded. The coding sheet and descriptions of ratings are shown in Appendix 1. Inter-rater reliability was calculated for all behaviors that had at least five occurrences. Reliabilities were: 0.71 for bodily anger, 0.79 for direct protest, 0.80 for sadness expression, 0.83 for anger expression, and 0.84 for indirect protest. Behavioral measures were averaged across epochs, and converted into z-scores. Table 1 presents the intercorrelations for the behavioral reactivity measures that were used in this study. For the purposes of data analyses, bodily and facial expressions were combined into composite scores for anger and sadness, and direct and indirect protest were combined into a composite score for protest.

Salivary Cortisol Collection. To measure changes in cortisol, one baseline and one post-stress sample were taken during the laboratory visit. The research assistant asked the child to chew on a cotton dental roll dipped in $1/64^{th}$ teaspoon of cherry Kool-Aid. After enough saliva had been absorbed into the cotton, it was extracted with a syringe and stored in a vial at -20 degrees Celsius until it could be assayed. Additionally, the mother was queried about environmental factors that could affect cortisol levels, such as child's sleep patterns, caffeine intake, and medication, on a structured health questionnaire. As changes in cortisol occur between fifteen and twenty minutes after exposure to a stressor, the baseline was taken within fifteen minutes of arrival to the laboratory to minimize changes due to fear or anxiety in the unfamiliar lab. To capture the peak cortisol level after the stressor, the reactivity sample was taken between fifteen and twenty minutes after completion of the task. Cortisol reactivity was calculated as the post-stressor level minus the pre-stressor level. This cortisol variable was log transformed prior to analyses to reduce skewness and kurtosis.

Maternal Psychiatric Diagnosis. Maternal diagnoses were assessed during the current laboratory visit using the Structured Clinical Interview for the DSM (SCID), administered by either a PhD level psychologist or a trained graduate student. Interviewers ask structured questions to determine lifetime history and the presence or absence of symptoms of Axis I disorders. The SCID also includes questions about psychiatric treatment history and basic demographic information such as race/ethnicity, age of parents, marital status, and number of persons in the house. The SCID is often considered the "gold standard" for the assessment of Axis I pathology (Shear et al., 2000). Interrater reliability for the current study was well established, with kappas for each mood disorder diagnosis ranging from .78-.90. 35 mothers met criteria for BD, 85 for MDD, and 32 did not have any Axis I diagnoses.

Paternal Psychiatric Diagnosis. Paternal diagnoses were provided by the mothers during the SCID. Mothers were asked about the father's history of BD and any other Axis I diagnosis as treated by a mental health professional.

Child Behavior Checklist (CBCL) (Achenbach & Rescorla, 2000). The CBCL assesses the level of behavioral problems in the past two months for children ages 1.5-5 years. The questionnaire includes 99 behavioral descriptors. The rater assigns a rating on a likert scale (0= not true), 1=sometimes true, 2=very true) according to how well the descriptor corresponds to the child's general behavioral functioning in the last 60 days. Higher scores indicate higher ratings of problems. The questionnaire yields overall scores for Total Problems, Internalizing Problems, and Externalizing Problems. In the current study, both mothers and alternative caregivers (e.g. father, teacher, grandmother) completed the CBCL. Standardized T-scores were used for data analyses.

Results

Assessing Potential Confounds

Prior to testing hypotheses, potential confounds were considered by assessing their associations with the dependent measures of interest. The confounds tested with anger, sadness, and protest were: child's gender, child's age, participation in a structured learning setting, number of hours the child slept the night before testing, the mother's education, the number of adults in the house, the number of children in the house, father's history of psychopathology, and mother's use of medications during pregnancy. Two significant confounds were found. Younger children were significantly more likely to show signs of protest (Pearson's $r(161)=-.28$, $p<0.001$) and the more adults in the home, the more likely the child was to show anger (Pearson's $r(159)=.19$, $p<.016$) and sadness (Pearson's $r(159)=.19$, $p<.018$). These confounds were included in analyses testing study hypotheses.

Confounds considered for cortisol reactivity related to both child and parental characteristics. For the children, gender, age, time since waking, time since brushing teeth, time since eating, recent tooth loss, exercise, illness with a cold, presence of mouth sores, caffeine intake, and ingestion of candy, liquids, steroids, antihistamines, stimulants, antidepressants, anxiolytics, allergy or cold medications were included. Parental and family characteristics included paternal diagnosis of any emotion/psychiatric disorder, maternal education, number of adults in the home, and number of children in the home. The only significant confounds were drinking (Pearson's $r(137)=.227$, $p<.007$) and recent tooth loss (Pearson's $r(137)=.243$, $p<.004$). As there were only three children with recent tooth loss they were excluded from analyses and drinking during the laboratory visit was controlled for appropriately when testing for differences in cortisol reactivity.

Correlations between Behavioral Reactivity and Cortisol

Preliminary analyses included a number of correlational analyses to test the relationship between measures. The first test analyzed the relationship between the measures of behavioral reactivity: anger, sadness, and protest. Anger was significantly correlated with protest (Pearson's $r(159)=.44$, $p<.0001$) and sadness (Pearson's $r(159)=.33$, $p<.0001$). Sadness and protest were also significantly correlated (Pearson's $r(159)=.38$, $p<.0001$).

Correlational analyses were also used to analyze the relationship between the measures of behavioral reactivity and ratings on the Child Behavior Checklist (CBCL). Mother ratings of externalizing problems were significantly correlated with anger (Pearson's $r(152)=.29$, $p<.0001$), sadness (Pearson's $r(152)=.16$, $p<.049$), and protest (Pearson's $r(154)=.20$, $p<.015$). Protest was also significantly correlated with alternate caregiver scores of externalizing problems (Pearson's $r(124)=.25$, $p<.005$), emotional reactivity (Pearson's $r(124)=.28$, $r<.002$) and internalizing problems (Pearson's $r(124)=.26$, $p<.003$)

Behavioral Reactivity

The first hypothesis was that the offspring of mothers with BD would display more behavioral reactivity in the form of anger, sadness, and protest compared to both controls, offspring of mothers with MDD and offspring of mothers with no Axis I diagnoses. The hypothesis was tested using a Univariate Analysis of Covariance (ANCOVA). Offspring of mothers with BD showed significantly higher levels of protest than the other two groups but there was no significant difference in anger or sadness (see Table 2).

Cortisol Reactivity

The second hypothesis was that offspring of mothers with BD would show higher cortisol reactivity compared to the controls. The hypothesis was tested using ANCOVA. No significant differences were found (see Table 2).

Maternal Diagnosis as a Moderator

The third hypothesis was that a maternal diagnosis of BD would moderate the relationship between behavioral and cortisol reactivity. A partial correlations test was conducted to examine relationships between the measures of behavioral reactivity and cortisol reactivity. As can be seen in Table 3, no correlations between behavior and cortisol were significant. Linear regressions were used to test maternal diagnosis as a moderator of the association between behavioral and cortisol reactivity, and no moderator effects were significant.

Discussion

The aim of the current research was to contribute to the literature on prodromal signs and symptoms for BD by studying high-risk preschool offspring of mothers with the disorder. Offspring at high risk for BD were compared to offspring of mothers with MDD and offspring of mothers with no Axis I diagnoses. The first hypothesis was that offspring of mothers with BD would show increased behavioral reactivity in the forms of anger, sadness, and protest. The hypothesis was partially supported, as offspring of mother's with BD showed significantly higher rates of protest but there were no significant differences in anger or sadness.

The findings of significantly increased protest but not anger or sadness support recent research and proposals that behavioral, rather than emotional dysregulation is a prodromal sign and core characteristic of childhood BD. Deficits in behavior regulation are evident in reports that high-risk offspring and children with BD have increased rates of behavior problems (Carlson & Weintraub, 1993) and disruptive behavior disorders, with some hypothesizing that the overlap in externalizing symptoms found in pediatric BD and Conduct Disorder (CD) may result in misdiagnoses of CD, or that CD may precede some cases of BD (Henin, et al., 2005; Akdemir & Gökler, 2008). Our measure of protest seemed to capture the commonly found externalizing

behaviors, as it had a significantly strong relationship with maternal and alternate caregiver ratings of externalizing problems and alternate caregiver reports of emotional reactivity. As one of the first reports to identify specific behavioral patterns in preschool children, our findings can potentially inform prevention and intervention strategies. For example, psychologists might focus on teaching children at high-risk to use more effective coping mechanisms than protest in stressful situations. Such treatments may also be beneficial to the family as protest increases the conflict and stress that exacerbate maternal psychological problems, thereby increasing the child's environmental risks for negative outcomes.

Externalizing problems in childhood, such as protest, are of particular concern as they are strong predictors of interpersonal deficits later in life (Ostiguy, et al., 2004), likely because of the effect they have on the child, mother, and parent-offspring relationship. Mothers whose psychological disorders already increase their susceptibility to stress will have a more difficult time coping with and addressing their offspring's externalizing behaviors. As a result, they may respond with negative modeling and a lack of support, failing to teach their children positive behavioral patterns and stress regulation tactics. While protest is already problematic in the preschool period due to the strain it places on the child-caregiver relationship, it will be especially ineffective in school, when the child's social network expands and expectations and pressures increase. Behavior problems and low agreeableness are not socially acceptable with peers and teachers, resulting in rejection, victimization, and other social failures (Jensen-Campbell, Adams, Perry, Workman, Furdella, & Egan, 2002). Therefore, it may be important to structure interventions based on high-risk preschoolers' propensity to use protest, with an emphasis on alternative stress responses that might improve the child's relationship with caregivers, peers, and others.

The second hypothesis was that offspring of mothers with BD would show significantly higher cortisol reactivity compared to the controls. The hypothesis was not supported, which is worth consideration and may be interpreted a number of ways, given that the cause of cortisol abnormalities remains unknown. The current study was the first to measure cortisol in such a young high-risk population for BD, so it is possible that the changes identified in high-risk adolescents and individuals with the disorder do not apply to young children (Ellenbogen, et al., 2004; Ellenbogen, Santo, Linnen, Walker, & Hodgins, 2010). These findings require further investigation, however, as high-risk adolescents only showed significant elevations in the afternoons and the current cortisol samples were collected in the morning. It is important to determine the onset of cortisol abnormalities, especially as they appear to precede diagnosis of BD and may be important prodromal signs for the disorder.

The current study is consistent with two proposed theories on the causes of cortisol reactivity in children. First, as neither offspring at risk for BD nor offspring at risk for MDD showed elevated cortisol, our research supports Ellenbogen and Hodgins (2009) findings that parental psychopathology does not predict HPA abnormalities. Maternal psychopathology may increase the likelihood of environmental risks by increasing stress and conflict (Chang et al., 2001), but ultimately, Ellenbogen and Hodgins (2009) found that the chaos of a home environment, defined by a lack of structure, organization, and consistency, was the strongest predictor of cortisol in middle childhood. The current sample of mothers was fairly high functioning and the majority of children lived in two-parent homes, so it is possible our sample lived in more supportive homes that served as a protective factor.

The second theory our research supports was proposed by Stansbury & Gunnar (1994), and explains that children will not show increased cortisol when they feel in control, which may

have been relevant given our sample's use of protest. Our findings, that children with high rates of externalizing problems responded to stress with negative behavior but not cortisol reactivity, resembles other reports that children with clinically significant externalizing behavior problems did not show increased cortisol in social situations. Based on Stansbury & Gunnar's (1994) theory, children with externalizing problems use aggression and problem behaviors to distract them from stressors or to create perceptions of control. Therefore, our sample of high-risk offspring may have gained the necessary feelings of control through their use of protest, thus suppressing harmful increases in cortisol during the laboratory stressor task. It may be important to measure cortisol levels for high-risk offspring in different social contexts to assess which behaviors and situations relate to cortisol reactivity.

The exploratory hypothesis was that maternal diagnosis would moderate the relationship between behavioral and cortisol reactivity. The hypothesis was not supported as there was a non-significant relationship between behavioral reactivity and cortisol and maternal diagnosis did not act as a significant moderator. It may be that other parent or child characteristics, rather than maternal diagnoses per se, influence the associations between cortisol and behavioral reactivity.

It is important to note that offspring at risk for BD and MDD largely showed similarities in behavior and cortisol. These findings are consistent with reports that offspring of parents with affective disorders are at similar risk for psychopathology, behavior, and attention problems (Carlson & Weintraub, 1993). Research should continue to compare the high-risk populations to distinguish between prodromal signs and symptoms specific to particular mood disorders.

Limitations

As early work in a new field of research, the current study had limitations that should be addressed in future studies. First, our sample was relatively high functioning with high rates of

maternal educational attainment, two-parent homes, and socioeconomic status, which all serve as protective factors for mother and offspring psychosocial functioning. Also, the current study only had six fathers with BD, and our analyses found that paternal BD may confound results. In conjunction with Chang et al.'s (2001) reports that children are at higher risk if they have two parents with mood disorders, it may be important for future studies to consider and measure the impact of paternal diagnosis. As we did not measure maternal behavior or chaos of the home environment and few children were at bilineal risk, it is possible that our sample was not representative of typical families with psychopathology, which would further explain the lack of significant results.

While we had a large sample, there were about twice as many offspring of mothers with MDD as there were offspring of mothers with BD and offspring of mothers with no Axis I diagnoses. More equal groups may better identify differences in symptoms between children at risk for BD and MDD. Finally, it is difficult to ethically induce stress, so it is possible our task did not sufficiently evoke behavioral or cortisol reactivity.

Future studies

As the causes of increased cortisol and its relationship with behavioral reactivity remains unclear, more research is needed on typically developing children and high-risk offspring. It appears that children may employ and benefit from different coping methods depending on whether they are at home or in a social situation, so their cortisol levels and behavioral patterns should be tested in different contexts. Regarding the relationship between cortisol and BD, more studies are needed that measure baseline and post-stressor cortisol in different age groups at different times of day, especially as abnormalities in high-risk populations may only appear in the afternoons (Ellenbogen & Hodgins, 2009).

Future studies on high-risk populations should compare the parenting behaviors of mothers with BD and MDD to evaluate the environmental risk of offspring that may account for their behavioral outcomes. It may also be important to measure paternal diagnosis in such studies, as it has been reported that children at bilineal risk have an even higher likelihood of negative outcome (Chang, et al., 2003). It would also be important to include assessments of the family environment to further substantiate Ellenbogen and Hodgins' (2004) findings that family environment is what predicts cortisol abnormalities in children, not parental psychopathology on its own. Finally, longitudinal studies that follow high-risk offspring from preschool would aid our understanding of development of the disorder, core symptoms, and protective and risk factors and should be pursued in the future.

Conclusions

Research on high-risk offspring for BD is new and limited, and the current study is one of the first to focus on preschool children. Studies on high-risk populations could help settle recent debates on the core symptoms of pediatric BD and guide intervention and treatment needed to address the increased prevalence of the disorder. The current report found that high-risk offspring employed higher rates of protest in response to stressors, which may be an indicator of externalizing problems. Future research is needed to identify other negative behavioral outcomes and their long-term effects. Additional research is also needed to explain the similarities and differences between offspring at risk for BD and MDD so that prevention programs can be designed and targeted appropriately for children at risk for mood disorders later in development.

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Appendix 1

Behavioral Reactivity Coding

Affective intensity was coded based on the number of facial regions that match the AFFEX description (0= no regions, 3= change in all 3 facial regions) with sadness operationalized by narrowed or squinted eyes, raised cheeks, the corners of the mouth pulled down and out (open or closed) with the upper lip protruding at the center, and the eyebrows raised at the inner corners and lowered at the outer corners with the skin below forming a triangle. Anger was operationalized by raised cheeks, a straight, angular, or tightly shut mouth, and drawn down brows that are either straight or slanting toward the center. Bodily signs of anger and sadness were also coded (0=not detectable, 1=detectable). Additionally, "protest," operationalized as direct refusal (0=no protest, 1= behavioral protest, 2= verbal protest, 3=both verbal and behavioral) and opposition, operationalized as indirect refusal (0=no opposition, 1= behavioral opposition, 2= verbal opposition, e.g. "I can't," "it's hard," etc.), were considered as signs of vocal and behavioral indications of emotion.

Coding was completed for the Green Circle Task using the coding sheet inserted below.

Green Circles Scoresheet EC 22

Subject #_____ Scorer_____

Subject Name _____ Date Scored _____ Tape # _____

Episode Order _____ Counter No. _____ Experimenter _____ D.O.V. _____

Baseline _____

Minute 1

10 secs	1	2	3	4	5	6
Time (Begin/End)						
Intensity of Anger Expression						
Intensity of Bodily Anger 0=no; 1=yes						
Intensity of Protest						
Intensity of Oppostion						
Intensity of Sadness Expression						
Intensity of Bodily Sadness 0=no; 1=yes						
Intensity of Resignation						

Minute 2

10 secs	1	2	3	4	5	6
Time (Begin/End)						
Intensity of Anger Expression						
Intensity of Bodily Anger 0=no; 1=yes						
Intensity of Protest						
Intensity of Oppostion						
Intensity of Sadness Expression						
Intensity of Bodily Sadness 0=no; 1=yes						
Intensity of Resignation						

Green Circles Scoresheet

Table 1.

Correlations Between Measures of Behavioral Reactivity

		Bodily Anger	Sadness Expression	Bodily Sadness	Indirect Protest	Direct Protest
Anger Expression	Pearson Correlation	.36**	.15**	.27**	.22**	.31**
Bodily Anger	Pearson Correlation	--	.04	.28**	.31**	.28**
Sadness Expression	Pearson Correlation	--	--	.43**	.32**	.18**
Bodily Sadness	Pearson Correlation	--	--	--	.23**	.25**
Indirect Protest	Pearson Correlation	--	--	--	--	.40**
Direct Protest	Pearson Correlation	--	--	--	--	--

*. Correlation is significant at the 0.05 level (2-tailed).

Table 2.

Maternal Diagnostic Group and Behavioral and Cortisol Reactivity

	BD Group Means	MDD Group Means	Control Group Means	F	*df*	*p* value
Anger	.00	.16	-.32	1.08	152	.342
Sadness	-.12	-.10	-.10	.00	152	.998
Protest	.51	-.08	-.47	3.23	152	.04
Cortisol	2.30	2.30	2.30	1.04	126	.357

Log transformed values of cortisol reactivity

Table 3.

Correlations between Behavioral and Cortisol Reactivity

Behavioral Reactivity Measure	Correlation with Cortisol	*p* value	*df*
Anger	.12	.17	121
Sadness	.04	.68	122
Protest	.01	.92	121