HHS Public Access

Author manuscript

Depress Anxiety. Author manuscript; available in PMC 2016 May 01.

Published in final edited form as:

Depress Anxiety. 2015 May ; 32(5): 325–334. doi:10.1002/da.22342.

Behavior and emotion modulation deficits in preschoolers at risk for bipolar disorder

Wan-Ling Tseng[a,*], **Amanda E. Guyer**[b,*], **Margaret J. Briggs-Gowan**[c], **David Axelson**[d], **Boris Birmaher**[e], **Helen L. Egger**[f], **Jonathan Helm**[g], **Zachary Stowe**[h], **Kenneth A. Towbin**[a], **Lauren S. Wakschlag**[i], **Ellen Leibenluft**[a], and **Melissa A. Brotman**[a]

[a]Emotion and Development Branch, National Institute of Mental Health, National Institutes of Health, Department of Health and Human Services

[b]Department of Human Ecology, Center for Mind and Brain, University of California, Davis

[c]Department of Psychiatry, University of Connecticut Health Center

[d]Nationwide Children's Hospital and The Ohio State University School of Medicine

[e]Western Psychiatric Institute, University of Pittsburgh

[f]Department of Psychiatry, Duke University

[g]Center for Mind and Brain, University of California, Davis

[h]Department of Psychiatry, University of Arkansas

[i]Department of Medical Social Sciences, Feinberg School of Medicine, Northwestern University

Abstract

Background—Bipolar disorder (BD) is highly familial, but studies have yet to examine preschoolers at risk for BD using standardized, developmentally-appropriate clinical assessment tools. We used such methods to test whether preschoolers at familial risk for BD have more observed difficulty modulating emotions and behaviors than do low-risk preschoolers. Identification of emotional and behavioral difficulties in at-risk preschoolers is crucial for developing new approaches for early intervention and prevention of BD.

Methods—Using the standardized Disruptive Behavior Diagnostic Observation Schedule (DB-DOS) protocol for preschoolers, we compared 23 preschoolers (M_{age}: 4.53±0.73 years; 18 males) with a first-degree relative with BD to 21 preschoolers (M_{age}: 4.65±0.84 years; 11 males) without a family history of BD. We characterized psychopathology in this sample using the Preschool Aged Psychiatric Assessment and behavioral and emotional problems using the Child Behavior Checklist.

Address correspondence to Wan-Ling Tseng, Ph.D., Building 15K Room 208, MSC 2670, 15K North Drive, Bethesda, MD 20892; wan-ling.tseng@nih.gov.

*Drs. Tseng and Guyer have equal contribution to this work as the first author.

Conflict of Interests: B. B. has or will receive royalties for publications from Random House, Inc. (New Hope for Children and Teens with Bipolar Disorder), Lippincott Williams & Wilkins (Treating Child and Adolescent Depression), and UpToDate. Z. S. reported grants from National Institutes of Health and personal fees from Oakstone CME, outside the submitted work; had previous relationships (prior to June 2008) with pharmaceutical companies – Pfizer, Glaxo-SmithKline, Wyeth, Lilly, BMS that included research grants, speakers bureau, and advisory boards. Other authors declared no conflict of interests.

Results—High-risk preschoolers demonstrated significantly more intense, pervasive, and clinically-concerning problems in anger modulation and behavior dysregulation on the DB-DOS than the low-risk group. High-risk relative to low-risk preschoolers, were also more likely to have maternal-reported anxiety and oppositional defiant disorders and internalizing and externalizing problems.

Conclusions—Clinically-concerning problems in anger modulation and behavior regulation, measured during standardized laboratory observation, differentiate preschoolers at high familial risk for BD from those at low risk. Investigation in a large longitudinal sample is critical for replication and for determining whether these observed behavioral differences can be reliably used as prodromal indicators of mood disorders.

Keywords

children; bipolar disorder; familial risk; irritability; inflexible behavior; diagnostic observation

Introduction

Bipolar disorder (BD) is both debilitating [1] and highly heritable [2]. Studies of youth at risk for BD by virtue of having an affected first-degree relative can provide the foundation for early intervention and, ultimately, prevention. Children at familial risk who are unable to modulate their irritability and anger may be at particularly high risk for BD [3]. Given the challenge of distinguishing clinically significant behaviors and emotions from normative variation in mood and behavior in young children [4, 5], there is a pressing need to identify clinically-concerning behaviors that flag prodromal indicators of an early mood disorder pathway.

In this study, we used the Disruptive Behavior Diagnostic Observation Schedule (DB-DOS), a standardized, structured observational paradigm to identify clinically-concerning irritable, inflexible, and resistant behaviors in preschoolers [6, 7]. The DB-DOS was specifically developed to differentiate the normative misbehavior of early childhood from clinically salient patterns. It has been shown to have clinical, predictive, and ecological validity [6]. Because of the high rates of oppositional defiant disorder (ODD) among BD youth, maladaptive responses to frustrating stimuli exhibited by BD youth [8], and the extreme emotion dysregulation that characterizes BD [9], it is particularly important to study whether preschoolers at risk for BD have difficulty modulating anger and regulating behavior.

Research documents increased emotional and behavioral problems, as well as psychopathology, among offspring of parents with BD [10–21]. These studies typically focus on school-age children and rely on diagnostic interviews or rating scales, administered to parents and usually children, rather than standardized observation of clinically-concerning behavior. Increasing evidence suggests that emotional and behavioral disorders exist and can be reliably identified in preschoolers [4, 22]. Attempts to extend work on BD into the preschool population highlight challenges inherent in studying emotion and behavior problems in preschoolers. First, until recently, rigorously-constructed, developmentally-sensitive instruments for diagnostic assessment of preschoolers have been lacking [4, 22]. Second, although disruptive and attention problems are the most common reasons for

preschool mental health referrals, age-appropriate development of autonomy and rapid behavioral change in preschoolers makes it difficult to distinguish normative from clinically-concerning misbehaviors [23, 24]. For example, BD involves emotional lability, but the normative increase in temper tantrums during early childhood makes distinguishing pathologic lability from typical low frustration tolerance challenging.

Emerging empirical studies have provided some data about the behavior and psychopathology of preschoolers at risk for BD [11, 12, 14, 21, 25–27]. Preschoolers with a family history of BD, compared to those whose parents are free of psychiatric illness or with non-BD psychopathology, have a higher rate of attention deficit hyperactivity disorder (ADHD) [14], more disruptive behavior and depression [11], more observed behavioral disinhibition [25], greater aggression and mood dysregulation [12], and more difficulty managing anger and hostile impulses during observed interactions with peers and unknown adults [26, 27]. In addition, preschoolers with major depressive disorder (MDD) plus a family history of BD, compared to those with MDD but no BD family history, are more likely to have the parent-reported symptom “restlessness/moves a lot” [21]. These studies relied on either parent report or behavioral observation, but none used both concurrently. Further, instruments used in previous research were not standardized and validated explicitly for distinguishing normative misbehaviors from clinically-concerning behaviors during the preschool period. An important next step is to collect information based on a developmentally-informed observational paradigm with standardized and validated codes that provide nuanced differentiation of clinically-concerning behaviors. This is particularly important in the context of this young high risk population where parental report may be biased by mood issues and low tolerance for misbehavior, and children are too young to report on their own behavior.

The goal of the present study is to ascertain whether observed behaviors distinguish preschoolers at familial risk for BD from low-risk preschoolers, with an eye towards reliable markers for detection of prodromal pathways. Here, we focus on and observe preschoolers’ responses during tasks designed to “press for” a range of clinically-concerning behaviors including temper loss, anger, low frustration tolerance, defiance, provocative, and inflexible behavior [24]. It is critical that observational methods capture the quality (e.g., intensity, flexibility) and pervasiveness (e.g., across contexts) of the behavior because these are key features that distinguish normative misbehavior from clinically significant behavior in the preschool period [24]. Indeed, tantrums are common in early childhood and typically last for a few minutes [28, 29]; prolonged, destructive, and daily tantrums, however, may index clinically-concerning emotional and behavioral problems [28].

In this study, we tested the main hypothesis that preschoolers at risk for BD, relative to low-risk preschoolers, would be more likely to demonstrate clinically-concerning problems modulating anger and regulating behavior in various observational contexts on the DB-DOS. We used the Child Behavior Checklist for ages 1½–5 (CBCL 1½–5) [30] and the Preschool Aged Psychiatric Assessment (PAPA) [31], a developmentally-appropriate, parent-report psychiatric assessment, to characterize preschoolers’ emotional and behavioral functioning dimensionally and categorically.

Methods

Participants

Participants were 44 children (29 male, 15 female) aged 3.45–5.96 years enrolled in a National Institute of Mental Health Intramural Research Program (NIMH-IRP) study. This study was approved by the IRB at the NIMH-IRP. Twelve participants were also enrolled in a study of bipolar offspring at the University of Pittsburgh; two participants were enrolled in a study at Emory University. Assessments for all children occurred at the NIMH-IRP; parents gave informed consent for their children to participate.

Twenty-three children were at risk (14 NIMH-IRP, 7 University of Pittsburgh, 2 Emory), and 21 were low-risk controls (16 NIMH-IRP, 5 University of Pittsburgh). Low-risk children were ascertained through community-wide advertisements. Groups did not differ significantly in the number of participants recruited per site, $\chi^2(2, N=44)=2.38$, $p=.30$. All were unrelated biologically and medication-naive.

At-risk participants had a parent ($n=17$; 11 BD I, 5 BD II, 1 BD-NOS) or sibling ($n=6$; 4 BD I, 2 BD II) in which a semi-structured interview confirmed a DSM-IV-TR BD diagnosis. For probands ≥18 years, the Structured Clinical Interview for DSM-IV-TR Axis-I Disorders-Patient Edition [29] or the Diagnostic Interview for Genetic Studies [32] was used. For probands <18 years, the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version [33] was used. Low-risk preschoolers had no first-degree relatives with an Axis-I diagnosis. Exclusion criteria for both groups included IQ <70 and pervasive developmental disorder.

Measures

Observational paradigm—The DB-DOS is a standardized observational paradigm for preschoolers, designed to assess clinically-concerning problems in Anger Modulation and Behavioral Regulation [5]. Behavior is assessed in three interactional contexts: *Parent:* parent interacts with child; *Examiner-Engaged:* examiner actively engages with the child; and *Examiner-Busy:* examiner is present, but busy with her own work. Within each interactional context there are various tasks, including “presses” which are designed to elicit a range of clinically-concerning behaviors. For example, in the Examiner-Engaged context, the examiner gives the child a bubble toy that does not work to “press for” frustration. The DB-DOS has good inter-rater and test-retest reliability [7] and validity [6] as a direct assessment of problems in regulation of irritability and behavior in early childhood.

The *Anger Modulation* domain assesses the quality of the child’s regulation of anger including ease of elicitation, intensity, and pervasiveness (Cronbach’s alpha = 0.85). The *Behavioral Regulation* domain taps the child’s resistant, provocative, and inflexible behaviors (Cronbach’s alpha = 0.80). Behaviors are coded as normative (0=normative behavior, 1=normative misbehavior) or clinically-concerning “problem” behaviors (2=of concern, 3=atypical). The DB-DOS paradigm was videotaped and coded. Coders were blind to the child’s risk status.

Diagnostic interview—The PAPA [31, 34], a standardized, structured parent interview for children 2–5 years old, was administered by a trained interviewer and subsequently coded. Diagnoses are made with DSM-IV-TR, using developmentally-appropriate diagnostic computer algorithms.

Emotion and behavior problems—We used the parent-reported CBCL 1½–5 [30] as a dimensional measure for preschool emotion and behavior problems, focusing on two broadband dimensions: internalizing (i.e., emotionally reactive, anxious/depressed, somatic complaints, withdrawn, and sleep problems subscales) and externalizing scales (i.e., attention problems and aggressive behavior subscales). T scores (M=50, SD=10) calculated based on age- and gender-referenced norms were used. Past studies have demonstrated the validity and reliability of the CBCL in clinical and research settings [35].

Cognitive functioning—The Differential Ability Scales (DAS)-Preschool version assessed the child's cognitive functioning [36] using a General Conceptual Ability score (M=100, SD=15).

Data Analysis

T-test and chi-square analyses (with Fisher's Exact Test adjustment for small cell sizes) were used to assess group differences in demographics, CBCL scores, PAPA diagnoses to characterize the sample. *T*-test and chi-square analyses were also used to examine group differences in the mean number of clinically-concerning problems on the DB-DOS, and the proportion of children with clinically-concerning problems within the observed anger modulation and behavior regulation domains respectively. Post-hoc analyses tested the effect of proband status (i.e., parent with BD vs. sibling with BD) and BD subtypes (i.e., BD I vs. BD II) on PAPA diagnoses, CBCL scores, and problems on the DB-DOS across contexts.

To test for group differences by contexts, we conducted zero-inflated Poisson regression [37, 38]. This type of regression model was used to account for the high rate of zero responses on the DB-DOS (33.3% for anger modulation; 38.6% for behavior regulation). Models were adjusted for gender and cognitive function and were fitted using Mplus [39] via robust maximum likelihood estimation to handle missing data (6.06%), while accounting for bias due to small sample size and violations of multivariate normality [40]. We report estimates from the model that examine differences in the number of anger modulation and behavior regulation problems between groups and across contexts, accounting for those children that do show such problems.

Results

Demographic and Diagnostic Characteristics

The high- and low-risk groups did not differ in demographics; however, the high-risk group had a lower IQ than the low-risk group (Table 1). The high-risk group had higher T scores on the CBCL internalizing and externalizing subscales than the low-risk group (Table 1). There was a significantly higher rate of anxiety disorders and ODD on the PAPA in high-

compared to low-risk children (Table 1). Due to this difference, additional post-hoc analyses were conducted to compare high-risk preschoolers with anxiety disorders to high-risk preschoolers without anxiety disorders on the DB-DOS problems across contexts. Post-hoc analysis was not conducted to compare high-risk preschoolers with or without ODD because only 5 high-risk preschoolers had ODD.

Participants from different sites did not differ in diagnoses, $F(2,41)=0.81$, $p=.45$. High-risk preschoolers with an affected parent ($n=17$) did not differ from those with an affected sibling ($n=6$) in the CBCL internalizing and externalizing subscales or in PAPA diagnoses ($ps>.16$). In addition, high-risk preschoolers with an affected parent or sibling with BD I ($n=15$) vs. BD II ($n=7$) did not differ in the CBCL internalizing and externalizing subscales or in PAPA diagnoses ($ps>.16$).

Clinically-Concerning Observed Behavior on the DB-DOS

Across DB-DOS contexts, the two groups differed significantly on the mean number of observed clinically-concerning problems in anger modulation and behavior regulation (i.e., the average summed of scores of 2 or 3). Specifically, high-risk, compared to low-risk, children had more clinically-concerning anger modulation problems ($M=1.09$, $SD=1.83$ vs. $M=0.10$, $SD=0.30$, respectively; $t[1, 23.30]=2.56$, $p=.017$). High-risk, relative to low-risk, children also had more observed clinically-concerning problems in behavior regulation ($M=1.39$, $SD=1.92$ vs. $M=0.38$, $SD=0.80$, respectively; $t[1, 30.02]=2.31$, $p=.028$).

The groups differed significantly in the proportion of children with clinically-concerning problems in both anger modulation and behavior regulation across DB-DOS contexts (Table 2). Nearly 22% of the high-risk group demonstrated two or more clinically-concerning problems in anger modulation, whereas none of the low-risk children showed such problems ($p=.05$; Table 2). In addition, 39% of high-risk vs. 9.5% of low-risk children demonstrated two or more clinically-concerning problems in behavior regulation ($p=.036$; Table 2).

At the item level, within the anger modulation domain and across contexts, a higher proportion of high- than low-risk children had clinically-concerning levels of anger intensity (tantrums, yelling, throwing things; 30.4% vs. 0%; $p=.006$; Table 3) and predominance (characteristically angry throughout tasks; 30.4% vs. 4.8%; $p=.048$; Table 3). Significant group differences were not found for the other anger modulation domain items.

Within the behavior regulation domain and across contexts, a higher proportion of high-than low-risk children had clinically-concerning levels of noncompliance intensity (39.1% vs. 9.5%; $p=.036$; Table 4) and noncompliance pervasiveness (21.7% vs. 0%; $p=.05$; Table 4). Significant group differences were not found for the other behavior regulation domain items.

High-risk preschoolers with an affected parent did not differ from those with an affected sibling in anger modulation and behavior regulation problems, at both the domain level and the item level ($ps>.09$). High-risk preschoolers with different proband diagnoses (BD I vs. BD II) also did not differ in anger modulation and behavior regulation problems, at both the domain level and the item level ($ps>.13$). In addition, high-risk preschoolers with and

without anxiety disorders did not differ in anger modulation and behavior regulation problems, at either the domain level or the item level (*p*s>.12).

Context-Specific Differences in Observed Behavior on the DB-DOS

Anger modulation—The behavior of high- and low-risk groups differed in the parent context (*p*=.01), but not in examiner-engaged (*p*=.74) or examiner-busy context (*p*=.12; Table 5). Specifically, relative to low-risk children, high-risk children showed more problems in anger modulation when interacting with their parent. Within group, low-risk children showed more problems, at a trend level, in the parent context (*M*=2.18) than in both the examiner-busy (*M*=1.23, *p*=.084) and examiner-engaged contexts (*M*=1.38, *p*=.097); behavior in the examiner-engaged and examiner-busy contexts did not differ (*p*=.78; Figure 1). Within-group comparisons in the high-risk children revealed more problems in the parent context (*M*=4.99) than in the examiner-engaged context (*M*=1.12, *p*<.01); problems in either the parent or examiner-engaged context did not differ from problems in the examiner-busy context (*M*=2.70, *p*s≥.10; Figure 1).

Behavior regulation—High- and low-risk children did not differ in any of the contexts (*p*s≥.13). Within group, low-risk children showed more problems in the parent context (*M*=2.64) than in the examiner-engaged context (*M*=1.05, *p*=.03); problems in either parent or examiner-engaged context did not differ from problems in the examiner-busy context (*M*=2.40, *p*≥.76; Figure 2). Within-group comparisons in the high-risk children revealed more problems in the parent context (*M*=4.72) than in the examiner-engaged context (*M*=1.95, *p*=.04); problems in either the parent or examiner-engaged context did not differ from problems in the examiner-busy context (*M*=2.75, *p*≥.83; Figure 2).

Discussion

This study used a developmentally-appropriate, standardized laboratory observation paradigm designed to press for qualitative differences in behavior and to distinguish normative misbehavior from problems in the regulation of irritability and behavior in preschoolers. We found that preschoolers at high risk for BD by virtue of having a parent or sibling with the illness were more likely than low-risk children to demonstrate clinically-concerning problems in anger modulation and behavior regulation. Problems in anger modulation manifested primarily as intense, dysregulated displays of anger and were present particularly when the child interacted with his/her parent. Problems in behavior regulation were characterized by intense, pervasive noncompliance across interactional contexts. This study illustrated that clinically-concerning problems in anger modulation and behavior regulation, measured using a standardized and developmentally-informed laboratory observation, can differentiate preschoolers at high risk for BD from those at low risk.

Interview-based diagnostic assessments and parent reports for preschoolers have validity and reliability [30, 31, 41]. Standardized observational clinical tools offer an integrative, objective weighting of multiple facets of behavior. Thus, this clinical method may capture nuances not discernible via categories of disorders based on parent interview [5] and may minimize potential informant bias associated with parental psychopathology [42]. Indeed, the DB-DOS allows for an objective assessment of behaviors across multiple contexts and

time [6, 7]. Clinical salience of the behavior is clearly defined in terms of *qualitative* deviations from the normative misbehavior and the *pervasiveness* across contexts during the preschool period [24].

Our study demonstrates that children with familial risk for BD have increased irritable and inflexible behavior (e.g., intense, pervasive anger dyscontrol and noncompliance). These findings add unique contribution to the literature because behaviors were identified using a developmentally-informed observational paradigm with standardized and validated codes for clinically-concerning behaviors. Our results are consistent with research documenting that preschoolers at familial risk for BD have difficulty managing hostility and aggression during social interactions [26, 27], show more disruptive or oppositional behavior [11], and display heightened emotional reactivity [12]. It is likely that as these high-risk preschoolers grow older, they may continue to show hostility and irritability [43]. Most importantly, these problems in anger modulation and behavior regulation mirror prior work on children diagnosed with BD. That is, relative to controls, preschoolers with BD display more intense and sustained emotional responses as well as difficulty regulating emotions over time [44], and school-age children with BD show more frustration and impaired adaptation to the task at hand [8]. Thus, an important question for future longitudinal research is whether these preschoolers at high risk for BD who exhibit problems modulating anger and behaviors are more likely to develop BD than at-risk preschoolers without such behaviors. Prior work with the DB-DOS has demonstrated its incremental clinical utility above and beyond DSM symptoms for prediction of longitudinal impairment [6]. Another important avenue for future studies is to investigate whether difficulty in anger modulation and behavior regulation is more prominent in a naturalistic setting such as home or school than in a laboratory setting, given that home and school contexts may be more emotionally charged and challenging. However, prior work with the DB-DOS suggests that variation on the DB-DOS context is associated with variation in naturalistic settings. In particular, observed problems in the parent context are associated with patterns specific to home settings, whereas observed problems in the examiner context are associated with patterns specific to the school setting, and pervasive problems across contexts are mirrored by pervasive problems as endorsed by both parents and teachers [45]. Not surprisingly, our at-risk group was differentiated particularly by problems in the parent context of the DB-DOS.

Problems as measured by the DB-DOS, anger modulation in particular, might indicate that a child has clinically-concerning irritability, defined as having developmentally inappropriate anger and temper outbursts and a low threshold for experiencing anger [9]. Whether these anger modulation problems are a manifestation of early mood dysregulation or a precursor to later BD or other types of psychopathology remains to be empirically tested. Indeed, this study cannot address whether the anger modulation problems observed in high-risk preschoolers are specific to risk for BD. Some previous research has reported that youth irritability (e.g., deficits in anger modulation), predicted adult anxiety and depression [46, 47]. More relevant to the current investigation, a recent study found that preschool irritability predicted depression and ODD across early childhood [48]. It is plausible that anger modulation problems may be indicative of a more general vulnerability for later psychopathology that is not specific to BD. Thus, in high-risk preschoolers, the extent to

which problems observed on the DB-DOS are associated with subsequent development of BD versus other mental illnesses should be addressed in future longitudinal research.

Consistent with the observational assessment that captured between-group differences in anger modulation and behavior regulation, high-risk preschoolers, relative to low-risk children, also had a higher rate of ODD based on a parent-reported psychiatric interview, as well as more parent-reported externalizing and internalizing problems based on a dimensional measure of emotion and behavior problems. The convergence of our results from different assessment methods further bolsters the finding that high-risk preschoolers exhibit difficulties modulating behaviors and emotions. Given the challenge regarding delineation of the boundaries between typical and atypical behavior during early childhood, multiple sources of information including standardized clinical observation and categorical and dimensional assessments of psychopathology may thus provide a more comprehensive and reliable measure of precursor behavioral patterns that manifest more subtly than full-blown psychiatric disorders [49].

Although offspring of parents with BD are at increased risk for developing BD [50], they are also at high risk for other psychopathology such as anxiety [14]. Indeed, in this study, high-risk preschoolers had a higher rate of anxiety disorders, compared to low-risk preschoolers; approximately 48% of our at-risk preschoolers met criteria for anxiety disorders. Some research has suggested that anxiety symptoms in early childhood may be prodromal and thus represent early markers of later BD in offspring of BD parents [51, 52]. Given the cross-sectional nature of this study, it is unclear if anxiety symptoms in the preschool years are indeed precursors of later BD. Prospective longitudinal research will be important in this regard.

Because of our small sample size, our findings should be considered preliminary. Since small sample sizes are more likely to be associated with type II than type I error, our negative findings should be interpreted with particular caution. In addition, our study design could not determine the extent to which the observed problems in anger modulation and behavioral regulation reflect biological vulnerability, the impact of the stress of having a parent or sibling with a psychiatric illness, the relatively high rates of anxiety disorders and ODD in the high-risk offspring, or a combination of these or other factors. Moreover, it is unclear the extent to which high-risk children's anger modulation difficulties are associated with bipolar parents' behaviors or mood state during the parent-child interactions. Of note, the modulation deficits were also present during the examiner context. In addition, some youth were at high risk by having a sibling proband; while our post-hoc analyses indicated that preschoolers with an affected parent did not differ from those with an affected sibling in anger modulation problems, these analyses may have been underpowered. Additional work should compare preschoolers at risk for BD with those at risk for non-BD psychopathology to disentangle the influence of familial BD from comorbid disorders on anger modulation and behavior regulation. Further, our post-hoc analyses showed that high-risk preschoolers with or without anxiety disorders had comparable levels of problems on the DB-DOS, suggesting that anxiety disorders did not impact our main findings. However, it should be noted that these post-hoc analyses were underpowered and thus susceptible to Type II error. Future research with a larger sample is needed to clarify the extent to which anxiety

disorders contribute to problems in anger modulation and behavior regulation. Finally, socio-economic status (SES) information was only available in 57% of the sample. Although high- and low-risk preschoolers did not differ in parental marital status, maternal education attainment, paternal education attainment, maternal occupational status or current occupation, and paternal occupational status or current occupation (*p*s>.05), high-risk preschoolers were more likely than the low-risk group to have families with lower household gross income (*p*=.04). Because of the small cell size, we did not conduct chi-square analyses to compare high- and low-risk groups with high vs. low household gross income on the DB-DOS. Future research is needed to rule out the contribution of SES variables, such as household gross income, to our findings.

In sum, the current study illustrated that preschoolers at high risk for BD show deficits in modulation of behavior and emotion. Importantly, this study demonstrated the utility of a diagnostic observation paradigm for characterizing preschool irritable and inflexible behaviors in a high risk sample in a developmentally sensitive and objective fashion. Early life difficulty in modulating one's anger and regulating behavior in keeping with social rules and norms across a range of tasks and interactional contexts requires further investigation as an early marker for BD. If the predictive utility of the DB-DOS for prediction of later BD is established, its use in high risk families may target young children in these families for prevention during the prodromal phase of the disease continuum. Identification of potential emotional and behavioral risk factors for BD in early childhood will provide important information to guide intervention, and possibly prevention, in young children at high risk for BD.

Acknowledgments

We gratefully acknowledge the important contributions of Alice Carter, Barbara Danis, Carri Hill, Sarah Horsey, Gordon Keeler, Evin Lawson, Bennett Leventhal, Jennifer K. Mendoza, Hannah Milch, Daniel S. Pine, Ed Potts, Gabriella Ra'anan, and Whitney Thomas. This research was supported by the National Institute of Mental Health (NIMH) intramural research program, a NARSAD Young Investigator Award (A. E. G.), NIMH grant MH068455 (L. W., M. B. G.), NIMH grant MH60952 (B. B.), the Walden W. and Jean Young Shaw Foundation (L. W.), and the Children's Brain Research Foundation (L. W.).

References

1. Merikangas KR, Jin R, He JP, et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch Gen Psychiatry. 2011; 68:241–251. [PubMed: 21383262]
2. Kieseppa T, Partonen T, Haukka J, et al. High concordance of bipolar I disorder in a nationwide sample of twins. Am J Psychiatry. 2004; 161:1814–1821. [PubMed: 15465978]
3. Fergus EL, Miller RB, Luckenbaugh DA, et al. Is there progression from irritability/dyscontrol to major depressive and manic symptoms? A retrospective community survey of parents of bipolar children. J Affect Disord. 2003; 77:71–78. [PubMed: 14550937]
4. Egger HL, Angold A. Common emotional and behavioral disorders in preschool children: presentation, nosology, and epidemiology. J Child Psychol Psychiatry. 2006; 47:313–337. [PubMed: 16492262]
5. Wakschlag LS, Leventhal BL, Briggs-Gowan MJ, et al. Defining the "disruptive" in preschool behavior: what diagnostic observation can teach us. Clin Child Fam Psychol Rev. 2005; 8:183–201. [PubMed: 16151617]

6. Wakschlag LS, Briggs-Gowan MJ, Hill C, et al. Observational Assessment of Preschool Disruptive Behavior, Part II: validity of the Disruptive Behavior Diagnostic Observation Schedule (DB-DOS). J Am Acad Child Adolesc Psychiatry. 2008; 47:632–641. [PubMed: 18434925]
7. Wakschlag LS, Hill C, Carter AS, et al. Observational Assessment of Preschool Disruptive Behavior, Part I: reliability of the Disruptive Behavior Diagnostic Observation Schedule (DB-DOS). J Am Acad Child Adolesc Psychiatry. 2008; 47:622–631. [PubMed: 18434926]
8. Rich BA, Schmajuk M, Perez-Edgar KE, et al. The impact of reward, punishment, and frustration on attention in pediatric bipolar disorder. Biol Psychiatry. 2005; 58:532–539. [PubMed: 15953589]
9. Leibenluft E, Blair RJ, Charney DS, et al. Irritability in pediatric mania and other childhood psychopathology. Ann N Y Acad Sci. 2003; 1008:201–218. [PubMed: 14998886]
10. Hirshfeld-Becker DR, Biederman J, Henin A, et al. Psychopathology in the young offspring of parents with bipolar disorder: a controlled pilot study. Psychiatry Res. 2006; 145:155–167. [PubMed: 17083985]
11. Radke-Yarrow M, Nottelmann E, Martinez P, et al. Young children of affectively ill parents: a longitudinal study of psychosocial development. J Am Acad Child Adolesc Psychiatry. 1992; 31:68–77. [PubMed: 1537784]
12. Maoz H, Goldstein T, Axelson DA, et al. Dimensional psychopathology in preschool offspring of parents with bipolar disorder. J Child Psychol Psychiatry. 2014; 55:144–153. [PubMed: 24372351]
13. Zahn-Waxler C, Mayfield A, Radke-Yarrow M, et al. A follow-up investigation of offspring of parents with bipolar disorder. Am J Psychiatry. 1988; 145:506–509. [PubMed: 3348454]
14. Birmaher B, Axelson D, Goldstein B, et al. Psychiatric disorders in preschool offspring of parents with bipolar disorder: the Pittsburgh Bipolar Offspring Study (BIOS). Am J Psychiatry. 2010; 167:321–330. [PubMed: 20080982]
15. DelBello MP, Geller B. Review of studies of child and adolescent offspring of bipolar parents. Bipolar Disord. 2001; 3:325–334. [PubMed: 11843782]
16. Dilsaver SC, Akiskal HS. Preschool-onset mania: incidence, phenomenology and family history. J Affect Disord. 2004; 82(Suppl 1):S35–43. [PubMed: 15571788]
17. Chang KD, Steiner H, Ketter TA. Psychiatric phenomenology of child and adolescent bipolar offspring. J Am Acad Child Adolesc Psychiatry. 2000; 39:453–460. [PubMed: 10761347]
18. Giles LL, DelBello MP, Stanford KE, et al. Child behavior checklist profiles of children and adolescents with and at high risk for developing bipolar disorder. Child Psychiatry Hum Dev. 2007; 38:47–55. [PubMed: 17160586]
19. Duffy A, Alda M, Hajek T, et al. Early stages in the development of bipolar disorder. J Affect Disord. 2010; 121:127–135. [PubMed: 19541368]
20. Diler RS, Birmaher B, Axelson D, et al. Dimensional psychopathology in offspring of parents with bipolar disorder. Bipolar Disord. 2011; 13:670–678. [PubMed: 22085480]
21. Luby JL, Mrakotsky C. Depressed preschoolers with bipolar family history: a group at high risk for later switching to mania? J Child Adolesc Psychopharmacol. 2003; 13:187–197. [PubMed: 12880512]
22. Angold A, Egger HL. Preschool psychopathology: lessons for the lifespan. J Child Psychol Psychiatry. 2007; 48:961–966. [PubMed: 17914996]
23. Campbell, S. Behavior problems in preschool children: Clinical and developmental issues. 2. New York: Guilford Press; 2002.
24. Wakschlag LS, Briggs-Gowan MJ, Carter AS, et al. A developmental framework for distinguishing disruptive behavior from normative misbehavior in preschool children. J Child Psychol Psychiatry. 2007; 48:976–987. [PubMed: 17914998]
25. Hirshfeld-Becker DR, Biederman J, Henin A, et al. Laboratory-observed behavioral disinhibition in the young offspring of parents with bipolar disorder: a high-risk pilot study. Am J Psychiatry. 2006; 163:265–271. [PubMed: 16449480]
26. Zahn-Waxler C, Cummings EM, McKnew DH, et al. Altruism, aggression, and social interactions in young children with a manic-depressive parent. Child Dev. 1984; 55:112–122. [PubMed: 6705614]

27. Zahn-Waxler C, McKnew DH, Cummings EM, et al. Problem behaviors and peer interactions of young children with a manic-depressive parent. Am J Psychiatry. 1984; 141:236–240. [PubMed: 6691484]
28. Wakschlag LS, Choi SW, Carter AS, et al. Defining the developmental parameters of temper loss in early childhood: implications for developmental psychopathology. J Child Psychol Psychiatry. 2012; 53:1099–1108. [PubMed: 22928674]
29. First, MB.; Spitzer, RL.; Gibbon, M., et al. Structured Clinical Interview for DSM-IV-TR Axis I Disorders-Patient Edition (SCID-I/P). New York: New York State Psychiatric Institute, Biometrics Research; 2002.
30. Achenbach, TM. Manual for the Achenbach System of Empirically Based Assessment Preschool Forms and Profiles. Burlington, VT: University of Vermont; 2001.
31. Egger HL, Erkanli A, Keeler G, et al. Test-Retest Reliability of the Preschool Age Psychiatric Assessment (PAPA). J Am Acad Child Adolesc Psychiatry. 2006; 45:538–549. [PubMed: 16601400]
32. Nurnberger JI Jr, Blehar MC, Kaufmann CA, et al. Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiative. Arch Gen Psychiatry. 1994; 51:849–859. discussion 863–844. [PubMed: 7944874]
33. Kaufman J, Birmaher B, Brent D, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry. 1997; 36:980–988. [PubMed: 9204677]
34. Egger, H.; Ascher, BH.; Angold, A. The Preschool Age Psychiatric Assessment: Version 1.4 (Unpublished interview schedule). Durham, NC: Center for Developmental Epidemiology, Department of Psychiatry and Behavioral Sciences, Duke University Medical Center; 2003.
35. Biederman J, Faraone SV, Doyle A, et al. Convergence of the Child Behavior Checklist with structured interview-based psychiatric diagnoses of ADHD children with and without comorbidity. J Child Psychol Psychiatry. 1993; 34:1241–1251. [PubMed: 8245144]
36. Elliott, C. Differential Abilities Scales (DAS): Introductory and technical handbook. New York: Psychological Corporation; 1983.
37. Cameron, AC.; Trivedi, PK. Regression Analysis of Clount Data. Cambridge: Cambridge University Press; 1998.
38. Long, JS. Regression Models for Categorical and Limited Dependent Variables. Thousands Oaks, CA: SAGE; 1997.
39. Muthén, LK.; Muthén, BO. Mplus User's Guide. Seventh. Los Angeles, CA: Muthén & Muthén;; 1998–2012.
40. Satorra, A.; Bentler, PM. Corrections to test statistics and standard errors in covariance structure analysis. In: von Eye, A.; Clogg, CC., editors. Latent variable analysis: Applications for developmental research. Thoudsand Oaks, CA: SAGE; 1994. p. 399-419.
41. Bufferd SJ, Dougherty LR, Carlson GA, et al. Psychiatric disorders in preschoolers: continuity from ages 3 to 6. Am J Psychiatry. 2012; 169:1157–1164. [PubMed: 23128922]
42. De Los Reyes A, Kazdin AE. Informant discrepancies in the assessment of childhood psychopathology: a critical review, theoretical framework, and recommendations for further study. Psychol Bull. 2005; 131:483–509. [PubMed: 16060799]
43. Farchione TR, Birmaher B, Axelson D, et al. Aggression, hostility, and irritability in children at risk for bipolar disorder. Bipolar Disord. 2007; 9:496–503. [PubMed: 17680920]
44. Luby JL, Tandon M, Belden A. Preschool bipolar disorder. Child Adolesc Psychiatr Clin N Am. 2009; 18:391–403. [PubMed: 19264269]
45. De Los Reyes A, Henry DB, Tolan PH, et al. Linking informant discrepancies to observed variations in young children's disruptive behavior. J Abnorm Child Psychol. 2009; 37:637–652. [PubMed: 19247829]
46. Brotman MA, Schmajuk M, Rich BA, et al. Prevalence, clinical correlates, and longitudinal course of severe mood dysregulation in children. Biol Psychiatry. 2006; 60:991–997. [PubMed: 17056393]

47. Stringaris A, Cohen P, Pine SD, Leibenluft E. Adult outcomes of youth irritability: a 20-year prospective community-based study. Am J Psychiatry. 2009; 166:1048–1054. [PubMed: 19570932]

48. Dougherty LR, Smith VC, Bufferd SJ, et al. Preschool irritability: Longitudinal associations with psychiatric disorders at age 6 and parental psychopathology. J Am Acad Child Adolesc Psychiatry. 2013; 52:1304–1313. [PubMed: 24290463]

49. O'Neill S, Schneiderman RL, Rajendran K, et al. Reliable ratings or reading tea leaves: can parent, teacher, and clinician behavioral ratings of preschoolers predict ADHD at age six? J Abnorm Child Psychol. 2014; 42:623–634. [PubMed: 24085388]

50. Luby JL, Navsaria N. Pediatric bipolar disorder: evidence for prodromal states and early markers. J Child Psychol Psychaitry. 2010; 51:459–471.

51. Duffy A, Alda M, Crawford L, et al. The early manifestations of bipolar disorder: a longitudinal prospective study of the offspring of bipolar parents. Bipolar Disord. 2007; 9:828–838. [PubMed: 18076532]

52. Shaw JA, Egeland JA, Endicott J, et al. A 10-year prospective study of prodromal patterns for bipolar disorder among Amish youth. J Am Acad Child Adolesc Psychiatry. 2005; 44:1104–1111. [PubMed: 16239857]

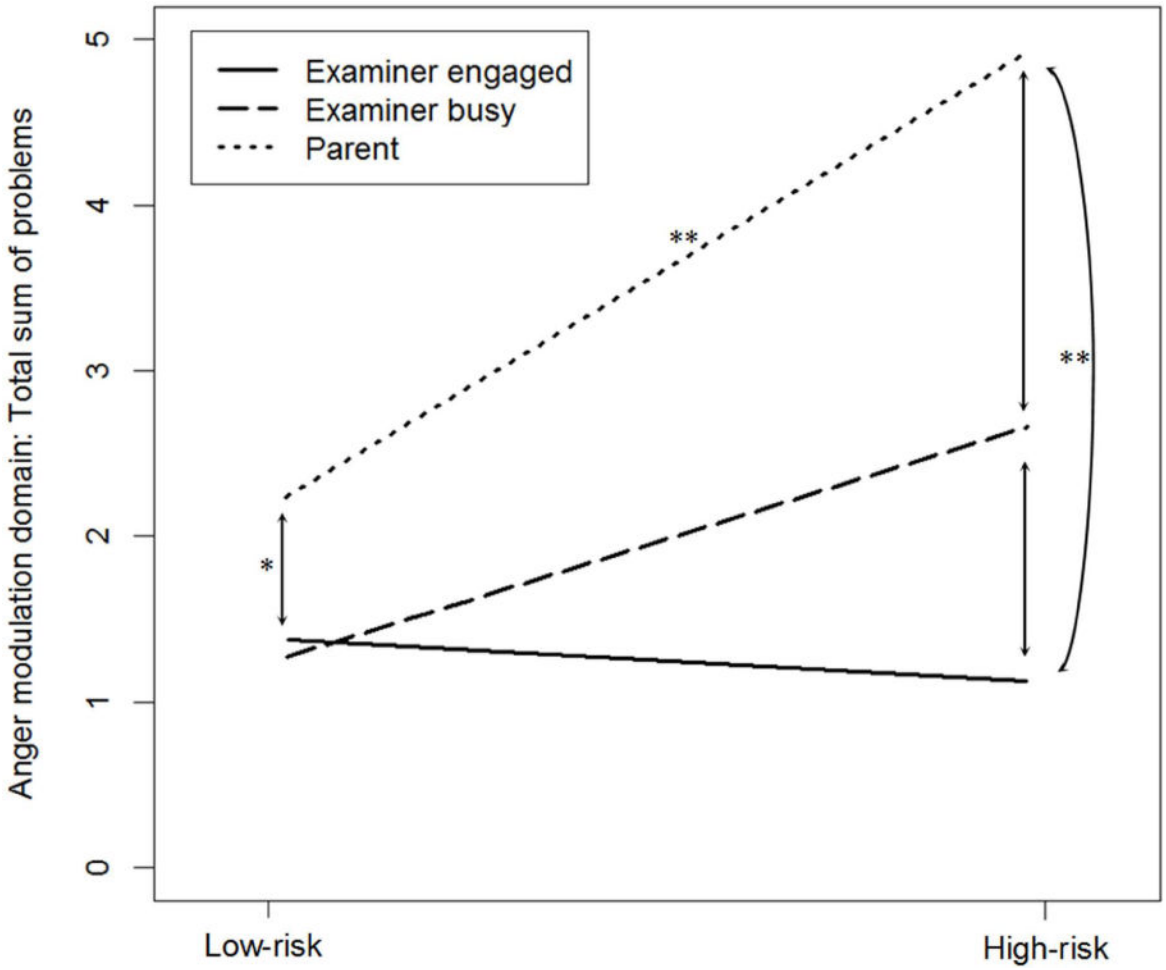

Figure 1.
Predicted anger modulation problems
Note. * $p < .10$; ** $p < .05$

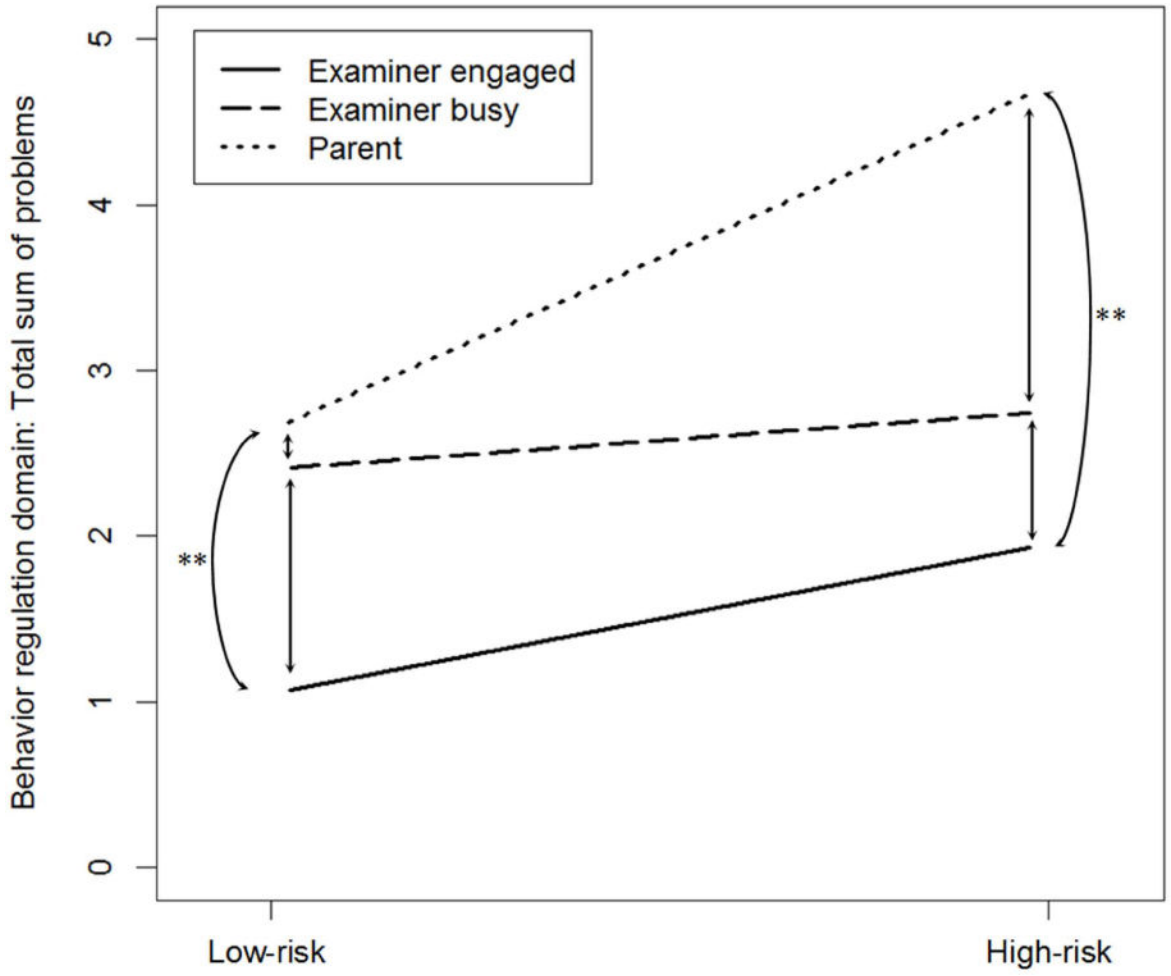

Figure 2.
Predicted behavioral regulation problems
Note. ** $p < .05$

Table 1

Demographic and diagnostic characteristics of the sample

	High-risk (*n*=23)	**Low-risk (*n*=21)**	**Statistic**
	Mean (SD)	Mean (SD)	
Age (yrs)	4.53 (0.73)	4.65 (0.84)	$t(42)=0.50$, $p=.62$
DAS general ability score	103.95 (18.71)	117.76 (15.11)	$t(41)=2.65$, $p=.01$
	% (n)	% (n)	
Sex (no. male)	78.3 (18)	52.4 (11)	$\chi^2(44)=3.27$, $p=.11$
Race (no. Caucasian)	87.0 (20)	71.4 (15)	$\chi^2(44)=1.63$, $p=.27$
Parent education (no. with college degree or higher)	68.4 (13)	89.5 (17)	$\chi^2(38)=2.53$, $p=.23$
CBCL	Mean (SD)	Mean (SD)	
Internalizing T score	49.00 (11.08)	40.31 (9.43)	$t(35)=2.52$, $p=.02$
Externalizing T score	52.33 (14.2)	40.25 (10.68)	$t(35)=2.84$, $p=.01$
PAPA diagnosis[a]	% (n)	% (n)	
Major depressive disorder	9.5 (2)	0	$\chi^2(42)=2.10$, $p=.49$
Any anxiety disorder	47.6 (10)[b]	4.8 (1)[c]	$\chi^2(42)=9.98$, $p=.004$
ODD	23.8 (5)	0	$\chi^2(42)=6.43$, $p=.017$
Conduct disorder	14.3 (3)	0	$\chi^2(42)=3.23$, $p=.23$
ADHD	14.3 (3)	0	$\chi^2(42)=3.23$, $p=.23$

Note. DAS = Differential Ability Scales; CBCL = Child Behavior Checklist; PAPA = Preschool Aged Psychiatric Assessment; ODD = Oppositional Defiant Disorder; ADHD = Attention-deficit Hyperactivity Disorder.

[a] Two high-risk children did not complete a PAPA assessment.

[b] included separation anxiety (*n*=2), generalized anxiety (*n*=2), specific phobia (*n*=7), and social phobia (*n*=2)

[c] specific phobia

Table 2

Observed problems in anger modulation and behavior regulation

	High-risk (*n*=23)		Low-risk (*n*=21)		Fisher's Exact Test
	≥ 2 clinically-concerning problems		≥ 2 clinically-concerning problems		
	No	Yes	No	Yes	
problems in anger modulation % (*n*)	78.3 (18)	21.7 (5)	100.0 (21)	0 (0)	χ^2 (44)=5.15, *p*=.050
problems in behavior regulation % (*n*)	60.9 (14)	39.1 (9)	90.5 (19)	9.5 (2)	χ^2 (44)=5.13, *p*=.036

Note. Observed problems were collapsed across all three DB-DOS contexts. Clinically-concerning problems received codes of 2 or 3. Total number of problems was 6 for anger modulation and 10 for behavioral regulation.

Table 3

Highest score of observed problems in anger modulation domain

	High-risk (*n*=23)		Low-risk (*n*=21)		
Items in anger modulation domain	**Normative range (0/1)**	**Clinically-concerning range (2/3)**	**Normative range (0/1)**	**Clinically-concerning range (2/3)**	**Fisher's Exact Test**
Intensity	69.6% (16)	30.4% (7)	100% (21)	0	χ^2 (44)=7.60, *p*=.006
Predominance	69.6% (16)	30.4% (7)	95.2% (20)	4.8% (1)	χ^2 (44)=4.86, *p*=.048
Ease of elicitation	91.3% (21)	8.7% (2)	100% (21)	0	χ^2 (44)=1.91, *p*=.49
Rapid escalation	91.3% (21)	8.7% (2)	100% (21)	0	χ^2 (44)=1.91, *p*=.49
Difficulty recovering from	87.0% (20)	13.0% (3)	100% (21)	0	χ^2 (44)=2.94, *p*=.23
Copes with frustration poorly	82.6% (19)	17.4% (4)	95.2% (20)	4.8% (1)	χ^2 (44)=1.74, *p*=.35

Note. Observed problems were collapsed across all three DB-DOS contexts.

Table 4

Highest score of observed problems in behavior regulation domain

	High-risk (*n*=23)		Low-risk (*n*=21)		
Items in behavior regulation domain	**Normative range (0/1)**	**Clinically-concerning range (2/3)**	**Normative range (0/1)**	**Clinically-concerning range (2/3)**	**Fisher's Exact Test**
Defiance	73.9% (17)	26.1% (6)	95.2% (20)	4.8% (1)	χ^2 (44)=3.73, *p*=.10
Noncompliance intensity	60.9% (14)	39.1% (9)	90.5% (19)	9.5% (2)	χ^2 (44)=5.13, *p*=.036
Noncompliance pervasiveness	78.3% (18)	21.7% (5)	100% (21)	0	χ^2 (44)=5.15, *p*=.05
Rule breaking – adult present[a]	73.9% (17)	26.1% (6)	85.7% (18)	14.3% (3)	χ^2 (44)=0.94, *p*=.46
Rule breaking – adult absent[a]	100% (20)	0	100% (19)	0	NA
Annoying behavior	100% (23)	0	100% (21)	0	NA
Physical aggression	91.3% (21)	8.7% (2)	100% (21)	0	χ^2 (44)=1.91, *p*=.49
Lying – examiner present[a]	100% (19)	0	100% (19)	0	NA
Lying – examiner absent[a]	100% (19)	5.0% (1)	100% (19)	0	χ^2 (39)=0.98, *p*=1.0
Social inflexibility	87.0% (20)	13.0% (3)	90.5% (19)	9.5% (2)	χ^2 (44)=0.14, *p*=1.0

[a]*Note*. Observed problems were collapsed across all three DB-DOS contexts, except for rule breaking and lying.

Table 5

Poisson coefficients for predicting anger modulation (AM) and behavioral regulation (BR)

Context	Outcome	Effect	Estimate	*z*	*p*
Examiner-Engaged	AM				
		Intercept	.32	1.00	.32
		Risk	−.21	−.31	.75
		Cognitive Function	.07	.32	.75
		Gender	.12	.36	.72
	BR				
		Intercept	.05	.12	.91
		Risk	.62	1.51	.13
		Cognitive Function	−.10	−.45	.65
		Gender	−.12	−.50	.62
Examiner-Busy	AM				
		Intercept	.21	.73	.47
		Risk	.78	2.04	.04
		Cognitive Function	−.13	−.82	.41
		Gender	.38	2.06	.04
	BR				
		Intercept	.88	.49	.63
		Risk	.14	.03	.98
		Cognitive Function	−.47	−.19	.85
		Gender	.35	.78	.43
Parent	AM				
		Intercept	.78	3.41	<.01
		Risk	.83	2.79	.01
		Cognitive Function	−.33	−2.73	.01
		Gender	−.05	−.33	.74
	BR				
		Intercept	.97	2.56	.01
		Risk	.58	1.38	.17

Depress Anxiety. Author manuscript; available in PMC 2016 May 01.

Context	Outcome	Effect	Estimate	*z*	*p*
		Cognitive Function	−.22	−1.44	.15
		Gender	−.03	−.11	.92

Note. Estimates are natural logarithm of the number of behaviors.