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Attention Bias to Threat Faces in Severe Mood Dysregulation

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Abstract

Background—We used a dot-probe paradigm to examine attention bias toward threat (i.e., angry) and happy face stimuli in Severe Mood Dysregulation (SMD) vs. healthy comparison (HC) youth. The tendency to allocate attention to threat is well established in anxiety and other disorders of negative affect. SMD is characterized by the negative affect of irritability, and longitudinal studies suggest childhood irritability predicts adult anxiety and depression. Therefore, it is important to study pathophysiologic connections between irritability and anxiety disorders.

Methods—SMD patients (N=74) and HC youth (N=42) completed a visual probe paradigm to assess attention bias to emotional faces. Diagnostic interviews were conducted and measures of irritability and anxiety were obtained in patients.

Results—SMD youth differed from HC youth in having a bias *toward* threatening faces ($p<0.01$). Threat bias was positively correlated with the severity of the SMD syndrome and depressive symptoms; degree of threat bias did not differ between SMD youth with and without co-occurring anxiety disorders or depression. SMD and HC youth did not differ in bias toward or away from happy faces.

Conclusions—SMD youth demonstrate an attention bias toward threat, with greater threat bias associated with higher levels of SMD symptom severity. Our findings suggest that irritability may share a pathophysiological link with anxiety and depressive disorders. This finding suggests the value of exploring further whether attention bias modification treatments that are effective for anxiety are also helpful in the treatment of irritability.

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Keywords

child and adolescent; anxiety; mood disorders; biological markers; cognition

Introduction

Severe irritability is one of the most common presenting complaints in child mental health clinics.[1–3] Emerging data suggest important, but relatively unexplored, associations between anxiety and irritability. For example, approximately half of youth meeting criteria for Severe Mood Dysregulation (SMD), a phenotype designed to capture severe and chronic irritability, also have an anxiety disorder.[3] In addition, epidemiologic studies suggest that chronic irritability in childhood predicts anxiety and depressive disorders in adulthood.[2, 4, 5] Taken together, these cross-sectional and longitudinal data indicate the need to study potential pathophysiological connections between chronic irritability and anxiety.

In patients with anxiety disorders, one of the most replicated pathophysiological findings involves the presence of threat bias, or the tendency to allocate attention toward threatening stimuli (e.g., angry faces) during the early, automatic stages of information processing.[6, 7] The dot probe paradigm assesses the effect of threat on attention allocation by briefly presenting paired threat-neutral stimuli (e.g., angry face paired with neutral face) followed by a response probe (small dot). Threat bias is assessed by measuring differences in reaction times to probes replacing threat rather than neutral stimuli.[8, 9]

Research suggests that threat biases may be present, not only in patients with anxiety disorders, but also in those with other disorders associated with negative-valence states, such as depression.[10–12] In fact, in such negative affective states, the magnitude of threat bias correlates with anxiety and depressive symptoms.[13, 14] Irritability is a negative valence state that is associated cross-sectionally and longitudinally with anxiety and depression.[2–5] Therefore, we anticipate youth with SMD, a condition characterized by severe irritability, would demonstrate a threat bias. Importantly, to the extent a threat bias is observed in SMD, it may not indicate that threat biases are *specific* to SMD, per se. Instead, it would be consistent with growing evidence that threat bias may be a marker of negative affectivity in a number of clinical conditions.[12, 13]

Here, we used a dot-probe paradigm to examine attention biases related to threat (i.e., angry) and happy face stimuli in SMD youth compared to healthy children and adolescents. Given associations among SMD, anxiety, and depression, coupled with evidence that threat bias may be a non-specific marker of negative affectivity, we hypothesized that youth with SMD would show a threat bias relative to healthy comparison youth. In addition, we expected that within the SMD sample, greater threat bias would be associated with more severe anxiety and mood (e.g., depression, irritability) symptoms; we also examined threat bias in SMD subjects dichotomized based on the presence or absence of an anxiety disorder or depression. Among SMD youth, we expected threat bias to be present in both medicated and medication-free youth. Finally, to determine whether the bias toward threat in SMD was specific to angry faces, we tested for attention bias to happy faces. As negative affectivity is more consistently associated with biases toward threat-related than positive stimuli,[15] we

did not expect to observe differences in happy bias between SMD and healthy comparison youth.

Methods

SMD (N=74) and healthy comparison (HC) youth (N=42) aged 7–17 years were recruited into an IRB approved study at the NIMH. Parents and children provided written informed consent/assent. Diagnoses were determined using the Schedule for Affective Disorders and Schizophrenia for School Age Children: Present and Lifetime Version (K-SADS-PL) [16], with supplemental SMD module. The K-SADS-PL interviews were conducted with children and parents separately and administered by clinicians with masters-level training or above ($\kappa > 0.9$); diagnoses were based on best estimate procedures. Diagnostic criteria for SMD include non-episodic irritability (i.e., irritable mood present for more than half the day, most days), excessive reactivity (3 or more outbursts/week) and hyper-arousal symptoms. Onset of symptoms must occur prior to age 12 years and there may not be a symptom-free period of more than two months. Symptoms cause impairment in multiple settings, with severe impairment in at least one setting. Children who display irritability only in the context of anxiety are excluded (e.g., a child with separation anxiety who becomes irritable only in the context of separations would not meet SMD criteria).[17] Exclusion criteria for all subjects included: IQ < 70, current substance abuse/dependence, pervasive developmental disorder, or psychosis. Healthy comparison subjects were free of any past or current Axis I disorder, and their first degree relatives were free of mood or anxiety disorders. Healthy subjects could not be taking any psychotropic medications, but SMD youth were accepted for study regardless of medication status. Full scale IQ was estimated using the Wechsler Abbreviated Scale of Intelligence (WASI).[18] Clinician-rated instruments, including the Mood Symptoms Questionnaire (MSQ), Pediatric Anxiety Rating Scale (PARS)[19], and Children's Depression Rating Scale (CDRS)[20], were completed with SMD youth within 48 hours of completing the dot-probe task. These clinician-rated instruments were not completed for HC youth. The MSQ indexes past-week mood and behaviors, and was developed by the Leibenluft group to assess the current severity of SMD symptoms, primarily irritability.[21] Factor analysis suggests that the MSQ captures irritability as a stable and robust factor; MSQ scores are strongly associated with irritability items on the Children's Depression Rating Scale,[20] and Young Mania Rating Scale[22], and MSQ scores differentiate SMD and bipolar disorder youth (Stringaris, unpublished data, available upon request). SMD youth were recruited nationally via advertisements targeting mental health support groups and clinicians. HC participants were recruited from the greater DC metro area through advertisements.

Participants completed a visual-probe paradigm used widely in research on pediatric and adult anxiety and other psychopathologies.[23–27] Face images from 80 actors are each presented twice across 160 trials. Photographs are displayed in pairs consisting of a neutral face and either a happy, neutral, or an angry (threatening) face.[8] Each trial begins with a 500 ms central fixation cross, followed by the 500 ms presentation of a face-pair. Immediately after the faces disappear, a single-asterisk probe appears for 1100 ms on the left or right side of the screen, in the space previously occupied by one of the faces. Subjects are instructed to press one of two keys (1 or 2) to indicate the probe location (right or left) as

quickly and accurately as possible. For emotional face trials, there are two conditions: (1) congruent, in which the probe replaces the emotional face (i.e., threat or happy); or (2) incongruent, in which the probe replaces the neutral face. We excluded data from incorrect trials and from trials with reaction time (RT) less than 150 ms or greater than 2.5 standard deviations above that individual's mean reaction time (8% of trials).[9] For the trials that included threat/neutral face-pairs, threat bias was calculated by subtracting mean RT on congruent trials from mean RT on incongruent trials.[9, 26] Positive numbers indicate a faster reaction time to probes that replace the threatening stimulus (i.e., the angry face) than to probes that replace neutral faces, and therefore indicate biased attention toward threat. Negative values of bias scores reflect biased attention away from threat relative to neutral faces. Similarly, data from trials that included happy/neutral face pairs was used to calculate happy bias.

Threat bias data were found to have a positive skew. Thus, we report median rather than mean threat bias scores as the measure of central tendency. Threat bias scores were logarithm transformed to fit a normal distribution for parametric analyses, and 65ms were added to each threat bias score prior to transformation to avoid taking the logarithm of a negative number. For our primary analysis, a t-test and Cohen's d compared log-transformed threat bias in SMD and healthy youth. Among SMD youth, Spearman correlations examined associations between threat bias and MSQ, PARS, and CDRS scores, as these clinical rating measures were not normally distributed. We conducted similar analyses to evaluate happy bias (happy bias scores followed a normal distribution and were not transformed prior to analysis).

We then performed two *post hoc* analyses designed to dissociate the effects of SMD, anxiety, depression, and medication on threat bias in youth with SMD. The first involved conducting a regression analysis, whereas the second set of analyses took a stratification approach. The regression analysis controlled for mood and anxiety disorder diagnoses, as well as medication status, and thus assessed the extent to which SMD uniquely contributes to threat bias. For the stratification analyses, we used three univariate analyses of variance (ANOVA). First, to test the effects of anxiety diagnoses, we compared log-transformed threat bias in SMD with co-occurring anxiety disorder (generalized anxiety, social phobia, and/or separation anxiety; SMD+ANX), SMD without anxiety disorder (SMD-ANX), and HC. Second, to test the effects of co-occurring major depressive disorder, we compared log-transformed threat bias in SMD with Major Depressive Disorder (SMD+MDD), SMD without Major Depressive Disorder (SMD-MDD), and HC. Finally, to examine the influence of medication status on threat bias, we compared un-medicated and medicated SMD youth and controls.

Results

Demographic and clinical characteristics

SMD (66.2% male; 13.1+2.3 years) and HC (52.4% male; 13.8+2.4 years) youth did not differ in age, gender, ethnicity, or IQ (Table 1). Most (63.5%) children with SMD had an anxiety disorder, most often generalized anxiety disorder (45.9%) or separation anxiety (31.1%). Other common DSM-IV diagnoses in the SMD group were attention deficit

hyperactivity disorder (85.1%) and oppositional defiant disorder (75.7%). More than half of SMD youth (59.5%) were taking at least one psychotropic medication at the time they completed the dot-probe task. Diagnostic data were available for all participants, while information on medication status ($N=73$) and clinical ratings were available for the majority of SMD youth (MSQ $N=72$, CDRS $N=72$, PARS $N=52$). One SMD patient was excluded from analyses because fewer than 70% of responses were correct.

Threat bias in SMD vs. HC

Median threat bias among SMD youth was 8.5 ms, with an interquartile range (IQR) of 27.6 ms. Median (IQR) threat bias among HC youth was -1.5 (26.3) ms. Log-transformed threat bias differed between SMD and HC [$t(114)=2.73$, $p=0.007$] with a medium effect size ($d=0.54$). SMD youth had a bias *toward* threatening faces. See Figure 1a.

Correlation between mood and anxiety measures and threat bias

Bias towards threat correlated positively with MSQ score [$(n=72)$, $\rho=0.30$, $p=0.01$] and CDRS score [$(n=72)$, $\rho=0.27$, $p=0.02$]. Threat bias did not correlate with PARS score [$(n=52)$, $\rho=0.23$, $p=0.10$]. MSQ, CDRS, and PARS scores all correlated moderately with each other [ρ 's $0.36-0.54$, $p<0.01$].

Regression analysis

We conducted a regression analysis to assess the effect of SMD on logtransformed threat bias, while taking account of the effect of three other potential predictor variables: depression and anxiety disorder diagnoses and medication status. When SMD was included as the sole predictor of threat bias, the regression model was significant, consistent with results reported earlier [$R^2=0.06$, $F(1,114)=7.47$, $p=0.007$]. The combination of the four predictor variables yielded an overall model that was not significant [$R^2=0.07$, $F(4,110)=1.90$, $p=0.11$]. However, consistent with the stratified analysis presented below, the presence of SMD was the most influential individual predictor (Beta=0.25, $p=0.07$). MDD diagnosis (Beta=0.05, $p=0.57$), anxiety disorder diagnosis (Beta=0.01, $p=0.93$), and medication status (Beta= -0.05 , $p=0.70$) did not predict threat bias.

Threat bias in SMD+ANX vs. SMD-ANX vs. HC

Median (IQR) threat bias was 8.4 (30.9) ms for SMD+ANX ($n=47$), 12.8 (29.3) ms for SMD-ANX ($n=27$), and -1.5 (26.3) for HC ($n=42$). Log-transformed threat bias differed among the three groups [$F(2,113)=3.73$, $p=0.03$]. *Post-hoc* t -tests revealed that threat bias was greater in SMD+ANX [$t(87)=2.55$, $p=0.01$, $d=0.54$] and SMD-ANX [$t(67)=2.2$, $p=0.04$, $d=0.53$] vs. HC youth. Threat bias did not differ between SMD+ANX and SMD-ANX youth [$t(72)=0.22$, $p=0.83$, $d=0.05$]. See Figure 1b.

Threat bias in SMD+MDD vs. SMD-MDD vs. HC

Median (IQR) threat bias was 8.1 (35.7) ms for SMD+MDD ($n=10$), 8.5 (29.0) ms for SMD-ANX ($n=64$), and -1.5 (26.3) for HC ($n=42$). Log-transformed threat bias differed among the three groups; $F(2,112)=3.89$, $p=0.02$]. *Post-hoc* t -tests revealed that threat bias was greater in SMD+MDD [$t(50)=2.0$, $p=0.05$, $d=0.62$] and SMD-MDD [$t(104)=2.6$,

$p=0.01$, $d=0.52$] vs. HC youth. Threat bias did not differ between SMD+MDD and SMD-MDD youth [$t(72)=0.5$, $p=0.59$, $d=0.17$].

Threat bias in unmedicated SMD vs. medicated SMD vs. HC

Median (IQR) threat bias was 8.4 (42.8) ms for un-medicated SMD ($n = 29$), 8.4 (27.8) ms for medicated SMD ($n = 44$), and -1.5 (26.3) for HC ($n = 42$). Log-transformed threat bias differed among the three groups; $F(2,112)=3.68$, $p=0.03$]. *Post-hoc* t-tests revealed that both un-medicated [$t(69)=2.4$, $p=0.02$, $d=0.56$] and medicated [$t(84)=2.4$, $p=0.02$, $d=0.51$] SMD youth showed significantly greater threat bias as compared to healthy controls. The presence of medication did not influence threat bias in SMD youth [$t(71)=0.4$, $p=0.7$, $d=0.01$].

Analyses of happy bias

Groups did not differ in bias toward or away from happy faces [mean (SD) happy bias SMD = -5.6 (31.9) ms; HC = -0.9 (25.6) ms; $t(114)=0.8$, $p=0.41$]. MSQ ($\rho=-0.07$, $p=0.54$), CDRS ($\rho=-0.05$, $p=0.68$) and PARS ($\rho=-0.01$, $p=0.95$) scores did not correlate with bias to happy faces.

Discussion

Our goal was to examine attention biases related to emotional face stimuli in SMD youth. We found that SMD youth demonstrate an attention bias toward threat. Among SMD youth, greater threat bias was associated with higher levels of SMD (e.g., irritability) and depressive symptoms. SMD youth with anxiety or without anxiety, and with or without depression showed greater threat bias than healthy comparison youth. In a regression analysis that controlled for cooccurring diagnoses and medication use, the presence of SMD predicted threat bias at the trend level. Thus, both regression and stratified analyses suggest that the threat bias we observed in a sample of children selected for severe and impairing irritability is not attributable solely to the co-occurrence of mood or anxiety disorders, or to medication status. Threat bias has been observed frequently in non-irritable patients with anxiety and, to a lesser extent, in non-irritable patients with depression. Therefore, our findings add to clinical and longitudinal data suggesting shared pathophysiology among anxiety, depression, and irritability, while also providing evidence that irritability itself plays a role in determining attention biases to threat.

The presence of threat bias in anxiety disorders is well established. Moreover, fMRI and MEG studies have defined the neural circuitry underlying threat bias in individuals with anxiety disorders.[9, 25, 28, 29] Although this remains to be established, similar neural circuitry may also be responsible for attention biases observed in other disorders of negative affect. Indeed, evidence suggests that disorders of anxiety and irritability may be mediated by common pathophysiological mechanisms. Anger and irritability engage the amygdala-hypothalamus-periaqueductal gray neurocircuitry, [30, 31] which also mediate fear and anxiety responses to threat.[32] While the precise neural mechanisms mediating SMD are unknown, outbursts may be related to abnormalities in basic threat perception or processing and/or they may reflect difficulties in top-down attentional control or other aspects of higher order mental processing. Our finding of threat bias in SMD youth suggests abnormalities in

the allocation of selective attention towards aversive information, and builds on previous ERP work demonstrating evidence of bottom-up processing deficits in SMD youth in the context of frustration.[33]. In addition to this pathophysiological evidence, epidemiologic studies have found childhood irritability is a risk factor for anxiety and depression in adolescence and young adulthood.[2, 4, 5, 34–38]. Given the clinical importance of anxiety, depression and irritability in youth, future work should continue to investigate the pathophysiological and clinical correlates of these distinct but related clinical constructs.

Attention biases are present, not only in individuals with anxiety disorders, but also in those with other disorders of negative affect, such as depression.[12, 13, 24, 25, 39–42] Our finding of a significant relationship between threat bias and SMD in youth (even those who do not have anxiety disorders or depression) extends previous research in suggesting that threat bias is not specific to anxiety disorders, and is found in other pediatric diagnoses associated with negative affect. These data also suggest that the role of depression and anxiety in threat bias in SMD is complex, and diagnostically subthreshold symptoms may contribute to threat bias in SMD. The role of negative affect, anxiety, and depressive symptoms in the development and maintenance of threat biases in youth with chronic and severe irritability merits further attention.

The presence of threat biases in chronic irritability may have potential treatment implications for individuals with negative valence states (e.g., depression, irritability, anxiety). Computer-based attention bias modification programs, designed to shift attention away from threat show promise in reducing residual depressive and anxiety symptoms in children and adults who demonstrate a bias towards threat at baseline.[7, 43–45] Evidence that greater threat bias is associated with greater SMD symptom severity suggests that attention bias modification may be a useful behavioral intervention to study in SMD youth.

Although threat bias has not been well studied in aggressive or irritable youth, other negative social information processing biases are well established in this population. Aggressive children tend to show a hostile attribution bias, i.e., they attribute hostile intent to the ambiguous actions of others.[46, 47] A core difference distinguishing hostile attribution bias from threat-related attention bias is that hostile attribution bias requires an interpretive element to be present. A hostile attribution bias refers to an increased tendency for an individual to interpret an ambiguous social stimulus to be hostile or threatening. Attention bias for threat refers to an increased tendency for an individual to attend preferentially to threat cues, relative to non-threat cues. It is assessed implicitly, generally by evaluation of the effect of threat (relative to non-threat) stimuli on response time or task performance. There is a dearth of research examining the relationship between hostile attribution bias and attention bias. Prior data in which SMD youth reported greater fear of neutral faces relative to healthy volunteers could be viewed as evidence of hostile attribution bias in SMD.[30] Thus, the current results extend what is known about conscious social-processing biases in irritable youth to encompass attention biases, which are objectively assessed from behavioral data, independent of introspection or self-report.

Future research using the dot-probe task and other social information processing paradigms will allow for a better understanding of the pathophysiology of irritability and its

relationship to anxiety and depression. A limitation of the current study is the small number of subjects in the SMD-ANX group and that we were unable to include a group of non-irritable, anxious youth. While data from other studies using similar dot-probe paradigms report threat bias scores that resemble those we observed in the SMD+ANX group,[39, 48] future studies should include anxious youth without irritability and larger number of anxious and non-anxious irritable children across a wide range of symptom severity. Similarly, we were limited by the small number of SMD+MDD youth in our sample, and the absence of a non-irritable depressed cohort. Given the high degree of inter-individual differences in threat bias scores, it is possible that our study was not sufficiently powered to detect subtle differences in threat bias between SMD youth with and without co-occurring anxiety or depressive disorders. Further study of attention biases in irritable youth without co-occurring anxiety or depression is especially warranted. This would allow for a more nuanced understanding of the specificity of threat bias in various negative affect states. It also would have been useful to have obtained continuous measures of irritability, anxiety, and depressive symptoms for all participants in both SMD and HC groups.

While we have noted that the presence of threat biases among anxious, irritable, and depressed youth may speak to a common pathophysiology underlying these negative affect states, it is also possible that disparate neural processes underlie the threat biases observed in SMD, anxious and depressed youth. Conducting functional neuroimaging studies to better elucidate potential pathophysiological links is an important direction for future research. In addition, most SMD youth have co-occurring attention deficit hyperactivity disorder (ADHD); another limitation of this study is the absence of an ADHD comparison group. Emotion-attention interactions in ADHD are not well understood, although other studies have not found evidence of threat bias in youth with ADHD or other disruptive behavior disorders.[13, 42, 49]

Including non-irritable youth with disruptive behavior disorders (DBDs), such as oppositional defiant disorder (ODD) and ADHD, would speak to the specificity of attention biases to irritability, rather than to ODD or ADHD. Unfortunately, we were not able to address this question in the current study because approximately 85% of SMD youth met criteria for either ODD, ADHD, or both, making any comparative analyses under-powered. Finally, most SMD youth in the current sample were medicated; however, differences in threat bias remained significant in the subset of unmedicated SMD patients relative to healthy comparison youth, suggesting that medication status does not account for threat bias among SMD youth.

In conclusion, we examined attention biases in SMD youth and found that SMD youth demonstrate an attention bias toward threat. Among SMD youth, threat bias is not influenced significantly by the presence of an anxiety disorder or depression, and greater threat bias is associated with greater mood dysregulation symptom severity. Thus, threat biases may be observed across a wide range of disorders associated with negative affect states, and irritability may play an important contributing role. These findings may offer insight into treatment for SMD, which currently lacks well-established effective treatments. Our results suggest that similar attentional mechanisms may underlie the development and maintenance of irritability and anxiety and suggest there may be value in studying attention

bias modification as a behavioral intervention to address irritability symptoms in SMD youth.

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Figure 1.

a. SMD Youth Show Attention Bias Toward Threat. Median (IQR) threat bias scores were 8.5 (27.6) ms for SMD ($n=74$) and -1.5 (26.3) ms for HC ($n = 42$). Log-transformed threat bias differed between SMD and HC [$t(114)=2.73$, $p=0.007$]. SMD youth had a bias *toward* threatening faces. Bars depict median threat bias scores with interquartile range and reflect original, rather than log-transformed, data.

b. Threat Bias Does Not Differ Between SMD Youth With and Without Co-Occurring Anxiety Disorder. Median (IQR) threat bias scores were 8.4 (30.9) ms for SMD+ANX ($n = 47$), 12.8 (29.3) ms for SMD-ANX ($n = 27$), and -1.5 (26.3) for HC ($n = 42$). Log-transformed threat bias differed among the three groups [$F(2,113)=3.73$, $p=0.03$]. Bars depict median threat bias scores with interquartile range and reflect original, rather than log-transformed, data.

Table 1

	Severe Mood Dysregulation	Healthy Comparison
<i>General Demographics</i>		
Number of Participants (# males)	74 (49)	42 (22)
Age, years (SD)	13.1 (2.3)	13.8 (2.4)
IQ (SD)	107.5 (12.9)	112.2 (14.2)
Ethnicity (N)		
Caucasian	59	32
African American	3	5
Asian	1	0
Latino	0	2
Mixed/Other	11	3
<i>Diagnostic Information [N (%)]</i>		
Generalized Anxiety Disorder	34 (45.9)	
Separation Anxiety Disorder	23 (31.1)	
Specific Phobia	11 (14.9)	
Social Phobia	9 (12.2)	
Obsessive Compulsive Disorder	1 (1.3)	
Any Anxiety Disorder	47 (63.5)	
Major Depressive Disorder	10 (13.5)	
Attention Deficit Hyperactivity Disorder	63 (85.1)	
Oppositional Defiant Disorder	56 (75.7)	
Eliminating Disorder	15 (20.3)	
Conduct Disorder	1 (1.3)	
<i>Medication Status</i>		
Medicated	44 (59.5)	
Unmedicated	29 (39.2)	
Unknown	1 (1.3)	
<i>Clinical Ratings [median (IQR)]</i>		
PARS (N=52)	14.0 (9)	
MSQ (N=72)	28.5 (10)	
CDRS (N=72)	27.5 (7)	

SMD youth and healthy controls did not differ in gender, age, IQ, or ethnicity.

Diagnostic information obtained using the Schedule for Affective Disorders and Schizophrenia for School Age Children: Present and Lifetime Version (K-SADS-PL). No children had diagnoses of Psychotic Disorder, Post Traumatic Stress Disorder, Adjustment Disorder or Panic Disorder. PARS, Pediatric Anxiety Rating Scale; MSQ, Mood Symptoms Questionnaire; CDRS, Children's Depression Rating Scale.