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Abnormal Neural Sensitivity to Monetary Gains Versus Losses Among Adolescents at Risk for Depression

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Abstract Major depressive disorder aggregates within families, although the mechanisms of transfer across generations are not well understood. In light of converging biological and behavioral evidence that depressive symptoms are associated with impaired reward processing, we examined whether adolescent girls with a parental history of depression would also exhibit abnormal reward sensitivity. We performed a negative mood induction and then recorded the feedback negativity, a neural index of reward processing, while individuals completed a gambling task. High-risk adolescents reported greater sadness following the mood induction compared to low-risk adolescents. Among the high-risk group, sadness was strongly associated with a blunted feedback negativity, even after controlling for baseline mood and trait neuroticism. This suggests that high-risk adolescents are more reactive to negative stimuli, which significantly alter neural sensitivity to monetary gains and losses. The feedback negativity might be used to identify information processing abnormalities in high-risk populations prior to the onset of a major depressive episode.

Keywords EEG · ERP · Depression · Adolescence · Reward · Feedback negativity

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Introduction

With a point prevalence of 2–4% among adults and a lifetime prevalence of 16%, major depressive disorder ranks among the world's most common illnesses (Kessler and Wang 2008). There is consistent evidence that depression aggregates within families, such that the odds of onset are three times greater in children with a parental history of depression (Goodman 2007; Hammen 2009), and recent approaches have sought to identify mechanisms by which this risk is transferred across generations. For example, it has been observed that depressed individuals exhibit reduced resting activity in left relative to right frontal cortical regions, which is interpreted in terms of a deficit in approach-related motivation and emotion (Davidson 1998; Debener et al. 2000). A similar frontal asymmetry has also been found in children of depressed mothers (Field et al. 1995; Jones et al. 2009; Tomarken et al. 2004), indicating that this deficit in approach motivation may predict vulnerability for depression as well.

In addition to studies relating neural measures of approach motivation to risk for depression, other research has focused on abnormalities in attention and memory, particularly with regard to emotional stimuli. In one early study, children of depressed mothers were found to recall fewer positive words in an experimental task compared to controls (Jaenicke et al. 1987). Similarly, Taylor and Ingram (1999) reported abnormal recall of emotional words among high-risk children, whereby maternal depression was associated with greater recall of negative words following a sad mood induction but not a neutral induction. It should be noted, however, that neither of these two studies controlled for history of depression within the high-risk children, leaving open the possibility that the reported recall biases reflect cognitive consequences of having

experienced a prior depressive episode—and not mechanisms of vulnerability per se. In a subsequent study that excluded children with a history of depression, risk status was associated with an attentional bias for emotional faces following a sad mood induction: high-risk children selectively attended to sad faces, whereas low-risk children selectively attended to happy faces (Joormann et al. 2007). Together, these studies suggest that recall and attentional biases in the processing of emotional information may differentiate high- from low-risk children.

It remains to be shown, however, whether abnormal reward processing may similarly act as a mechanism for depression vulnerability. This topic is relevant in light of converging biological and behavioral evidence that depressive symptoms are associated with reduced sensitivity to rewarding stimuli. For example, healthy individuals reliably exhibit a response preference toward rewarding stimuli in signal-detection tasks, but depressed individuals do not (Henriques and Davidson 2000; Pizzagalli et al. 2008). Similarly, non-depressed individuals exhibit an increase in relative left frontal brain activity when anticipating a reward during a laboratory gambling task, whereas depressed individuals do not (Shankman et al. 2007). Extending this focus on reward sensitivity in depression to a pediatric sample, Forbes and colleagues (2007) conducted a study in which 11 year-old children completed a laboratory gambling task that included trials varying in both reward magnitude and reward probability. Non-depressed children exhibited a response style that was significantly influenced by the magnitude of potential rewards, whereas currently depressed children were insensitive to reward magnitude. In each of these studies, abnormalities in reward sensitivity were observed among individuals with current depressive symptoms. To assess for the possibility that abnormal reward sensitivity may also relate to vulnerability for depression, it is of interest to expand this research focus to include never-depressed individuals within high-risk families.

In the current study, we sought to pursue this question and examine how abnormal reward processing is associated with familial risk for depression. We chose to focus on the feedback negativity (FN), a neural response in the event-related potential (ERP) that differentiates feedback indicating favorable from unfavorable outcomes. Specifically, the FN is numerically more negative for unfavorable outcomes (e.g., monetary loss), and more positive for favorable outcomes (e.g., monetary gain; Gehring and Willoughby 2002; Miltner et al. 1997). That is, the FN is observed as a relative negativity in the ERP following losses compared to gains, a difference which peaks approximately 300 ms following feedback presentation and is maximal at fronto-central recording sites. The FN has been interpreted as reflecting the early, binary evaluation of outcomes as either better or worse than expected, and it has been suggested that variation in FN magnitude indicates phasic changes in dopaminergic signals within the mesocorticolimbic reward circuit when reward prediction errors occur (Holroyd and Coles 2002). Consistent with this perspective, the FN has been shown to be increased in response to unexpected feedback (Bellebaum et al. 2010; Hajcak et al. 2007; Holroyd et al. 2003; Potts et al. 2006) and to track the relative valence of outcomes within the immediate context (Holroyd et al. 2006, 2004). By contrast, the FN appears to be insensitive to reward magnitude (Hajcak et al. 2006; Sato et al. 2005; Yeung and Sanfey 2004). One outstanding issue is whether changes in the FN reflect neural activity related to positive feedback, negative feedback, or both (Holroyd 2004). In fact, two recent studies demonstrated that variation in the FN may be primarily due to rewards (Foti et al. 2011; Holroyd et al. 2008). As such, quantifying the FN as the numerical difference between negative and positive feedback provides a measure of the differentiation between monetary gain and loss—that is, neural sensitivity to outcome valence (Dunning and Hajcak 2007; Hajcak et al. 2007; Holroyd et al. 2008; Miltner et al. 1997).

In two recent studies examining individual differences in neural responses elicited by environmental feedback, the FN recorded during a laboratory gambling task was used to identify abnormal reward sensitivity in relation to disturbances in mood. In an initial study, the severity of self-reported depressive symptoms over the prior week predicted a reduction in FN magnitude in a non-clinical sample. Because the FN was scored as the difference between negative and positive feedback, this association indicated that greater symptom severity predicted less neural differentiation between monetary gains and losses (Foti and Hajcak 2009). In a follow-up study, the link between depressive symptoms and variation in the FN was related to state variation in negative affect. Following a sad mood induction in a sample unselected for depression history, increases in reported sadness predicted a reduction in FN magnitude, even after controlling for baseline differences in depressive symptoms (Foti and Hajcak 2010).

It remains to be shown, however, whether this reduction in the FN during negative mood states may be moderated by risk for depression. According to the diathesis-stress model of depression vulnerability, individuals at elevated risk ought to exhibit information processing abnormalities (i.e., abnormal FN magnitude) when experiencing negative mood states. That is, environmental stressors that elicit negative affect are thought to prime depressogenic schemas and alter the processing of emotional stimuli. Indeed, in laboratory settings, sad mood inductions have been used as mild stressors to elicit attentional, recall, and interpretive biases in the processing of affective information among high-risk individuals (for a review, see Scher et al. 2005). One possibility, then, is that a negative mood state will elicit

reduced sensitivity to gains versus losses among individuals at increased risk for depression, such that the inverse association between FN magnitude and sadness will be enhanced within this group. We sought to address this question in the present study by inducing a sad mood and then recording the FN in never-depressed adolescent females either with or without a parental history of depression. As observed in previous studies, we expected that increases in reported sadness following the mood induction would predict a reduced FN (i.e., a smaller difference between gains and losses). Additionally, we predicted that this reduction in FN magnitude with increasing sadness would be moderated by risk status, such that high-risk adolescents would exhibit a greater reduction in sensitivity to gains versus losses compared to low-risk adolescents. This would be reflected by a significant interaction between risk status and state sadness in predicting the FN.

Methods

Participants

The target population consisted of female adolescents between the ages of 15 and 17 residing in Suffolk County, New York. In light of consistent evidence that major depression is more common among females and that this gender difference emerges during adolescence (Piccinelli and Wilkinson 2000), this target population was chosen to maximize the power to detect group differences related to depression vulnerability. Candidates for the study were randomly selected from a commercial mailing list of local families with girls in this age range. The use of commercial lists is cost-effective, and this approach yields samples that are largely comparable to random digit dialing across a wide range of demographic and health-related variables (Wilson et al. 1999). An initial phone interview was conducted with each adolescent and her mother to determine eligibility. In four cases, it was not possible to interview the mother (e.g., deceased, not living with the adolescent). In these cases, the interview was instead conducted with the father. The presence of a lifetime major depressive episode was assessed during this screening interview using the nine-item mood module from the Patient Health Questionnaire (PHQ-9; Kroenke et al. 2001), which is described further below. The mother answered questions regarding her own history and that of the father, and the PHQ-9 was also administered separately to the adolescent. In light of evidence that both maternal and paternal depression are risk factors for depression in offspring (Klein et al. 2005), the inclusion criterion for the high-risk group was the presence of a major depressive episode in one or both parents. The inclusion criterion for the low-risk group was the absence of any major depressive episode in both parents. To be eligible for the current study, none of the adolescents could have had history of a major depressive episode.

Attempts were made to contact a total of 825 parents by telephone. 199 parents (24%) completed the interview and confirmed that their daughter was eligible and willing to participate in the study. The remaining families were lost for the following reasons: non-working number (6%), ineligible (23%), refused prior to determining eligibility (22%), eligible but refused (2%), and unable to reach (23%). Eighty-six adolescents participated in the current study (46 low-risk, 40 high-risk). Two were excluded from analysis due to poor quality ERP data, one was excluded due to incomplete self-report data, and two were excluded for being statistical outliers (see Data Screening, below), leaving 44 low-risk and 37 high-risk adolescents in the final sample. None of the adolescents discontinued their participation once the procedures had begun, and they each received $55 for their participation, including $5 as winnings from the gambling task. All participants provided written informed consent to participate in the study, and this research was formally approved by the Stony Brook University Institutional Review Board.

Background Measures

History of Depression The presence of a lifetime major depressive episode was assessed using the PHQ-9 (Kroenke et al. 2001), a measure which taps each of the nine depressive symptoms defined in the *DSM-IV*. A recent meta-analysis concluded that the PHQ-9 has a sensitivity of 0.77 and a specificity of 0.94 (Wittkampf et al. 2007), and the PHQ-9 has been shown to be highly concordant with structured clinical interviews when assessing lifetime depression (Cannon et al. 2007) and also change in depression diagnosis over time (Lowe et al. 2004). The responder is instructed to recall the 2 weeks of lowest mood in their life and report on the frequency of nine symptoms, with each symptom rated on a four-point scale (0=*not at all*, 1=*several days*, 2=*more than half the days*, and 3=*nearly every day*). To qualify as a major depressive episode, a total of five items must be rated with a 2 or 3 for that single two-week period, and one of those items must be either anhedonia or depressed mood.

Current Depressive Symptoms To rule out the influence of sub-threshold symptoms, current (2-week) depressive symptoms were assessed using the General Depression scale from the Inventory of Depression and Anxiety Symptoms (IDAS; Watson et al. 2007). This scale consists of 20 items rated on a five-point scale (ranging from 1=*not at all* to 5=*extremely*), and has been shown to have excellent internal consistency

among clinical and non-clinical samples, as well as good convergent and discriminant validity.

Personality Traits Trait neuroticism, reflecting the tendency to experience negative emotions such as sadness, was evaluated using the 44-item version of the Big Five Inventory (John and Srivastava 1999). The neuroticism subscale consists of eight items rated on a scale of one (strongly disagree) to five (strongly agree), and has satisfactory reliability (α=0.84). Insofar as elevated levels of neuroticism predict the onset of a major depressive episode among high-risk populations (Kendler et al. 2004), this measure was included to rule out the possibility that the association between the FN and negative affect is better accounted for by third-variable personality characteristics.

Mood Induction

The sad mood induction paradigm was based on the guidelines provided by Rottenberg et al. (2007) for using film clips to elicit discrete emotional states. The mood induction consisted of two five-minute film clips and a song that was played in the background while participants completed a series of computer tasks. The film clips used were from *The Champ* and *My Girl*, and the song used was Gabriel Faure's *Piano Quintet No. 1 in D Minor (Op. 89)*. Upon completing the computer tasks, a pleasant mood was induced in all participants using an amusing film clip.

To assess current mood throughout the experiment, the valence scale of the Self-Assessment Manikin was used (Lang 1980). The adolescents were asked to rate their current emotional state ranging from one (maximally happy) to nine (maximally sad). This measure was administered at five points throughout the experiment: before and after each of the two film clips, and again at the conclusion of the experiment. For the current study, the two ratings of interest were those taken at baseline and immediately prior to the gambling task (i.e., following either the first or second film clip, depending on the time of the gambling task for each adolescent).

Task

The task was administered on a Pentium D class computer, using Presentation software (Neurobehavioral Systems, Inc., Albany, CA) to control the presentation and timing of all stimuli. On each trial, the adolescents were shown a graphic displaying two horizontally adjacent doors and chose which door they wanted to open (the graphic occupied approximately 6° of the visual field vertically and 8° horizontally). They were instructed to press the left or right mouse button to choose the corresponding door. Following each choice, a feedback stimulus informed them whether they won or lost money on that trial. A green '↑' indicated a correct guess and a gain of $0.50, while a red '↓' indicated an incorrect guess and a loss of $0.25. Gains were twice as large as losses to approximately equate subjective value (Tversky and Kahneman 1992). All cues and feedback were presented against a black background and occupied approximately 3° of the visual field vertically and 1° horizontally. At the end of each trial, they were presented with the instruction 'Click for the next round'. All participants were informed that they would actually receive the total money earned during the task, and that they should use any response strategy possible to maximize gains. The task consisted of 40 trials, with positive feedback given on exactly 20 trials (i.e., 50%). Feedback was presented in a random order for each adolescent.

The order and timing of all stimuli were as follows: (i) the graphic of two doors was presented until a response was made, (ii) a fixation mark (+) was presented for 1000 ms, (iii) a feedback arrow was presented for 2000 ms, (iv) a fixation mark was presented for 1500 ms, and (v) 'Click for the next round' was presented until a response was made.

Procedure

At the beginning of the laboratory session, all adolescents completed the BFI. Following a brief description of the experiment, electroencephalograph (EEG) sensors were attached and the mood induction was introduced. The adolescents then viewed the first film clip (with pre- and post- mood ratings) and performed two computer tasks. Participants then viewed the second film clip (with pre- and post- mood ratings) and completed two additional computer tasks. The order of the four computer tasks was randomized for each adolescent, such that the gambling task may have occurred at any of the four possible times: either the first or second task following a film clip, for either the first or second clip. The three other computer tasks are unrelated to the aims of the current study, and will be presented separately. In brief, these other tasks consisted of two attentional bias tasks (one using emotional faces, and a second using emotional scenes) and a speeded response (i.e., flanker) task. To familiarize the adolescents with the gambling task, they were first given a practice block containing five trials. They then performed the main task; the running total of money earned was presented at the halfway point. Following the final laboratory task, participants completed a final mood rating, watched a pleasant film clip, and were paid their winnings (i.e., $5.00).

Psychophysiological Recording and Data Reduction

The continuous EEG was recorded using a custom cap (Cortech Solutions, Wilmington, NC) and the ActiveTwo

BioSemi system (BioSemi, Amsterdam, Netherlands). The signal was pre-amplified at the electrode with a gain of one; electroencephalogram data was digitized at 24-bit resolution with a sampling rate of 512 Hz using a low-pass fifth order sinc filter with a half-power cutoff of 102.4 Hz. Recordings were taken from 34 scalp electrodes based on the 10/20 system (including FCz and Iz), as well as two electrodes placed on the left and right mastoids. The electrooculogram was recorded from four facial electrodes: two approximately 1 cm above and below the left eye, one approximately 1 cm to the left of the left eye, and one approximately 1 cm to the right of the right eye. Each electrode was measured online with respect to a common mode sense electrode that formed a monopolar channel.

Off-line analysis was performed using Brain Vision Analyzer software (Brain Products, Munich, Germany). All data were re-referenced to the average of the two mastoids and band-pass filtered with cutoffs of 0.1 and 30 Hz. The EEG was segmented for each trial, beginning 200 ms before feedback onset and continuous for 800 ms following feedback onset. Each trial was corrected for blinks and eye movements using the method developed by Gratton and colleagues (1983). Specific channels were rejected in each trial using a semi-automated procedure, with physiological artifacts identified by the following criteria: a voltage step of more than 50.0 μV between sample points, a voltage difference of 300.0 μV within a trial, and a maximum voltage difference of less than 0.50 μV within 100-ms intervals. Additional artifacts were identified using visual inspection.

Stimulus-locked responses were averaged separately for each type of feedback (gain or loss) and the activity in the 200-ms window prior to feedback onset served as the baseline. For each adolescent, the feedback negativity was quantified as the mean activity in a 50-ms window surrounding the peak negative deflection in the difference wave (loss minus gain) at a pooling of Fz/FCz, where the difference was numerically maximal across the full sample. A difference wave approach was chosen due to the fact that it remains unclear to date whether variance in FN magnitude primarily reflects neural activity elicited by losses, gains, or both. The FN has previously been interpreted as reflecting neural activity related to unfavorable outcomes (Holroyd and Coles 2002), but more recent evidence suggests that variation in the FN may actually be driven primarily by neural activity related to favorable outcomes, such as monetary reward (Foti et al. 2011; Holroyd et al. 2008). As recommended by Luck (2005), scoring the difference between losses and gains isolates variation in the waveform due to feedback valence, regardless of whether it is due to negative feedback or positive feedback (cf., Hajcak et al. 2007). Therefore, more negative values for this difference indicate greater differentiation in the ERP between gains and losses and greater sensitivity to outcome valence. As this difference goes to zero, it indicates reduced differentiation in the ERP and blunted sensitivity to outcome valence.

Data Screening and Statistical Analysis

Grubbs' Test (1969) was used to investigate for the presence of outliers in the key study variables: feedback negativity, neuroticism, baseline sadness, post-induction sadness, and the product of risk status and post-induction sadness (i.e., the interaction term). Considering the full sample of 83 adolescents, one low-risk participant had statistically deviant data for baseline sadness ($z=3.72$, $p<0.05$). Inspection of this individual's data revealed that she reported a high level of sadness at baseline (a value of eight) which decreased following the sad mood induction (to a value of five). Additionally, one high-risk participant had statistically deviant data for the product term of risk status and post-induction sadness ($z=3.77$, $p<0.05$). Inspection of this individual's data revealed that she reported the minimum level of sadness (a value of one) both at baseline and following the sad mood induction, which was deviant relative to the rest of the high risk group. None of the remaining study variables contained an outlier (all p's>0.05). All statistical tests were conducted twice, first including these two outliers and then again after excluding them. These two approaches yielded similar results in terms of the direction and significance level of effects; for clarity, all statistical values reported below are for the cases where the outliers were excluded, unless otherwise specified.

Group means on continuous study variables were compared using independent samples t-tests with Levene's test for the equality of variances, and group frequencies on categorical variables were compared using Pearson's chi-square test. Interactions between categorical variables were tested using mixed-model ANOVA. Associations between continuous study variables were measured using Pearson's correlation and multiple linear regression. For tests using linear regression, interactions involving continuous variables were examined first by centering the variables and then adding the product term as an additional predictor beyond the main effects. Multicollinearity was assessed by examining the bivariate correlations (cutoff of 0.90) and the variance inflation factors (cutoff of 10). Effects of sadness were examined using post-induction sadness ratings while including baseline sadness as a covariate, thereby allowing for inferences about sadness while holding baseline mood constant. Statistical analysis was performed using SPSS (Version 17.0; SPSS, Inc., Chicago, IL). All statistical tests used a two-tailed significance threshold of $p<0.05$.

Results

Participant Characteristics

Demographic characteristics of the low- and high-risk groups are presented in Table 1. There were no significant group differences in age or ethnicity (all p's>0.15). The high-risk adolescents reported significantly higher levels of neuroticism than the low-risk adolescents ($t(79)=2.27$, $p<0.05$). No significant group differences were observed on the remaining personality traits or on current depressive symptoms (all p's>0.20).

Sadness Ratings

Results from the sadness ratings taken at baseline and following the negative mood induction are presented in Fig. 1. A mixed-model ANOVA yielded a main effect of time ($F(1,79)=409.406$, $p<0.001$), indicating that individuals reported increased sadness overall following the induction. This effect was qualified by a significant interaction with risk status ($F(1,79)=5.28$, $p<0.05$), and follow-up comparisons confirmed that after the induction, high-risk adolescents reported greater levels of sadness compared to low-risk adolescents ($t(79)=3.14$, $p<0.01$). At baseline, however, sadness ratings did not significantly differ between the two groups ($t(79)=0.96$, $p=0.33$). In other words, while the sample became sadder on average following the negative induction, this effect was enhanced among the high-risk group compared to the low-risk group.

Table 1 Characteristics of participants

Characteristic	Group			
	Low risk (n=44)		High risk (n=37)	
	n	%	n	%
Parental history of depression				
Mother only	0	0.0	21	56.8
Father only	0	0.0	10	27.0
Both parents	0	0.0	6	16.2
Caucasian	40	90.9	34	91.9
	M	SD	M	SD
Age (years)	15.91	0.88	16.16	0.90
Neuroticism	21.93	6.66	25.00*	5.26
Extraversion	29.14	6.40	30.89	5.61
Agreeableness	36.64	5.46	35.65	4.87
Conscientiousness	32.86	5.83	31.84	4.84
Openness	37.61	6.37	38.00	5.60
Depressive symptoms	36.27	11.13	37.46	9.95

*Group difference significant at $p<0.05$

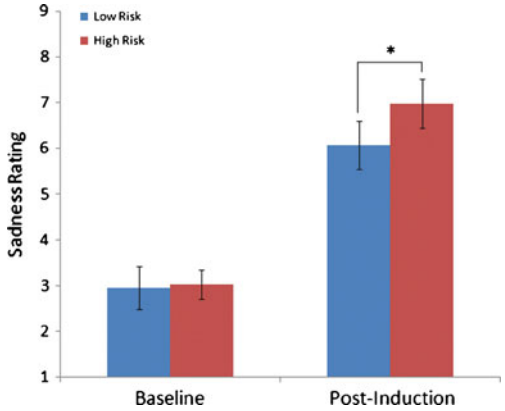

Fig. 1 Sadness ratings at baseline and following the negative mood induction for the low- and high-risk groups. *Error bars* represent 95% confidence intervals. *$p<0.05$

Across the entire sample, neuroticism predicted higher levels of sadness both at baseline ($r=0.32$, $p<0.01$) and after the induction ($r=0.40$, $p<0.001$). Lastly, both neuroticism and risk status appeared to predict reactivity to the negative induction independently: When entered as simultaneous predictors in a linear regression, both risk status ($\beta=0.24$, $p<0.05$) and neuroticism ($\beta=0.24$, $p<0.05$) significantly predicted post-induction sadness, controlling for baseline sadness. The Risk × Neuroticism interaction, however, was not significant ($p=0.40$).

Feedback Negativity

The FN was significantly predicted by post-induction sadness ratings ($r=0.32$, $p<0.01$) but not baseline sadness, risk status, neuroticism, or depressive symptoms (all p's> 0.50). ERPs as a function of sadness ratings and risk status are presented for the full sample in Figs. 2 and 3, respectively. Because a larger FN is numerically negative, the positive correlation with sadness ratings indicates that greater sadness following the induction was associated with less differentiation between gains and losses. Using linear regression, the inverse association between the FN and post-induction sadness persisted after controlling for baseline sadness, risk status, neuroticism, and depressive symptoms ($\beta=0.40$, $p<0.01$).

To examine whether this main effect of post-induction sadness was moderated by risk status and by neuroticism, the product terms were added to the regression. There was evidence of a significant Sadness × Risk interaction (Outliers Included: $\beta=0.18$, $p=0.10$; Excluded: $\beta=0.27$, $p<0.05$), but no 2- or 3-way interactions with neuroticism (all p's>0.40). The Sadness × Risk interaction remained in the same direction with or without the outliers, but the effect was stronger after excluding the two deviant participants. This interaction indicates that the association between post-induction sadness and the FN was stronger among high-

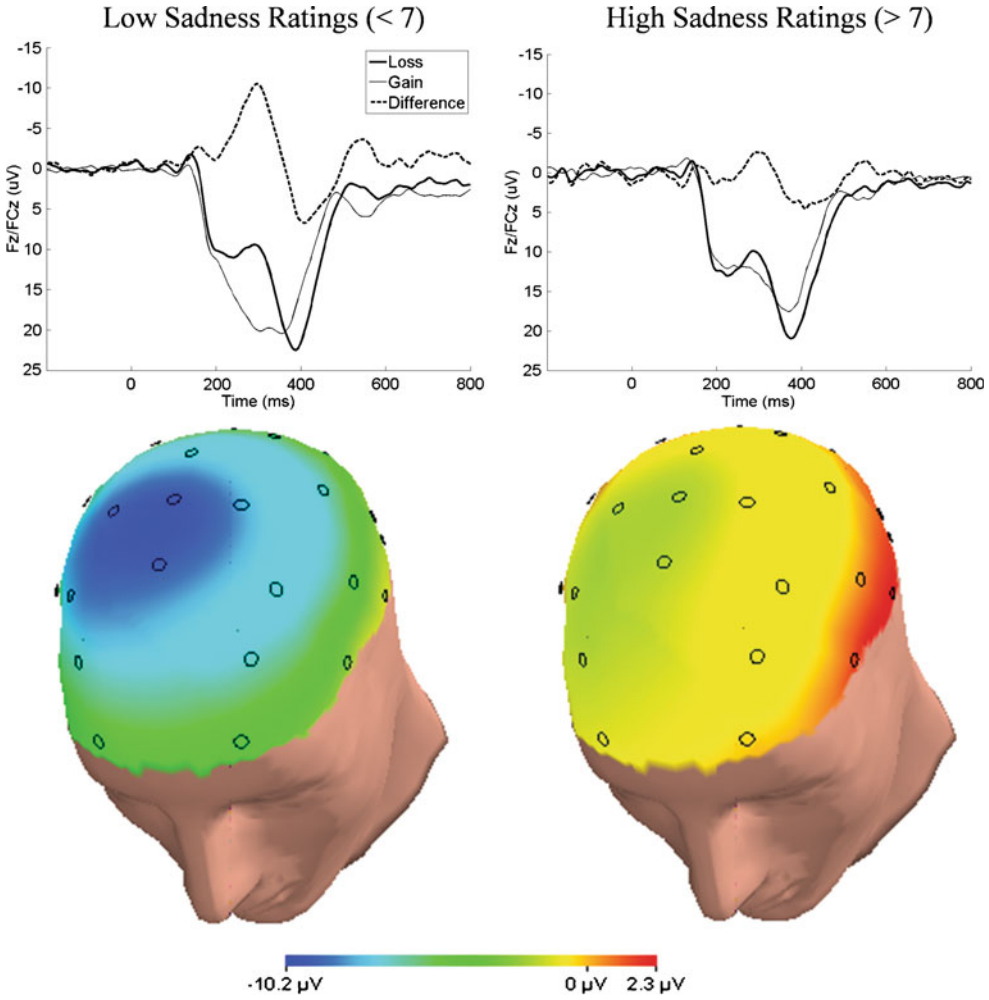

Fig. 2 Top: Event-related potentials for gain and loss trials, presented separately for participants reporting low and high levels of post-induction sadness (median=7). Bottom: Scalp topographies of the difference between losses and gains from 275 to 325 ms, where the feedback negativity is maximal

risk adolescents (r=0.79, p<0.001) compared to low-risk adolescents (r=0.18, p=0.24); in other words, the significant product term means that the correlations between sadness and the FN are significantly different between high- and low-risk adolescents. The regression lines for each group (based on the full regression equation and excluding outliers) are presented in Fig. 4.[1] The pattern of the interaction at low levels of sadness, however, must be interpreted with caution. After removing the outliers, there were no high-risk participants in the sample with a post-induction sadness rating of less than four. With that caveat in mind, we performed two additional tests to examine the possibility that this interaction was primarily driven by *greater* discrimination of gains from losses among high-risk adolescents at low levels of sadness. T-tests were calculated predicting FN magnitude with risk status separately for the lower (<6) and upper (>7) quartiles of post-induction sadness. Neither difference was statistically significant (both p's>0.10).

Lastly, we examined the influence of task order. When the gambling task occurred after the second film clip, there was a robust association between sadness and the FN regardless of whether it was the first (n=20, r=0.55, p<0.05) or second task (n=23, r=0.45, p<0.05). When the gambling task occurred after the first film clip, however, there was a robust association when it was the second (n=15, r=0.58, p<0.05) but not the first task (n=23, r=−0.03, p=0.89). This indicates that the influence of state sadness on FN magnitude did not emerge until after the first computer task, but after that the effect was relatively stable. Based on this pattern, we repeated the regression analysis described above after excluding those individuals who completed the gambling task first, leaving a subsample of 58 participants (high risk: n=29, low risk: n=29). As before, the FN was inversely related to post-induction

[1] As a point of comparison, we repeated then regression analysis using sadness as a difference score, post-induction minus baseline, rather than covariation. The pattern of results was similar, with sadness change inversely related to FN amplitude across the whole sample at the bivariate level (r=0.28, p<0.01) and after adjusting for risk status, neuroticism, and depressive symptoms (β=0.31, p<0.01). This association was again stronger among the high-risk group (r=0.51, p<0.01) compared to the low-risk group (r=0.31, p<0.05), although the difference between the correlation coefficients was less pronounced and the interaction term was not statistically significant (β=0.11, p=0.33).

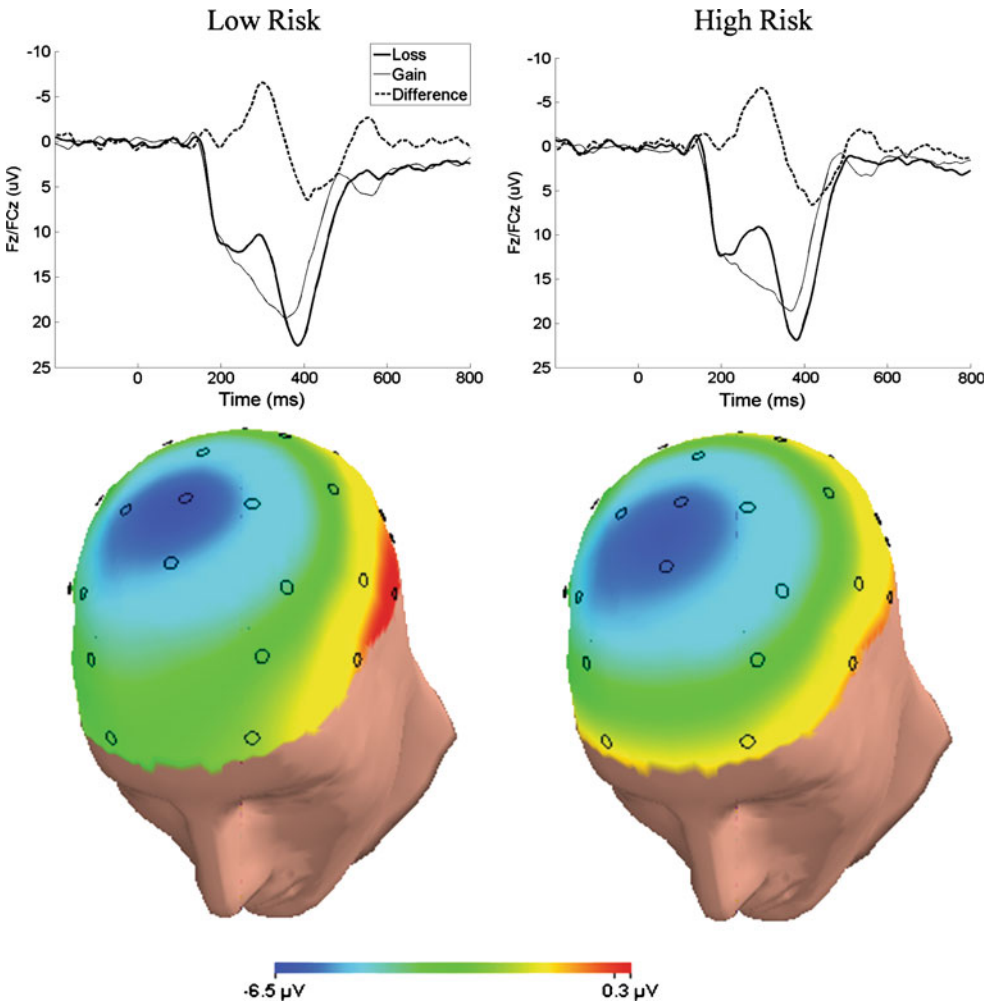

Fig. 3 Top: Event-related potentials for gain and loss trials, presented separately for low- and high-risk adolescents. Bottom: Scalp topographies of the difference between losses and gains from 275 to 325 ms, where the feedback negativity is maximal

sadness after controlling for risk status, baseline sadness, neuroticism, and depressive symptoms (β=0.64, p<0.001). Adding the product terms to the regression again yielded a significant Sadness × Risk interaction (β=0.31, p<0.01), but no interactions with neuroticism (all p's>0.20).

Discussion

Consistent with two prior studies (Foti and Hajcak 2009, 2010), the FN was found to be inversely related to negative affect—greater levels of sadness following a negative mood induction predicted less neural differentiation between gains and losses. The present study also sheds new light on this effect by demonstrating that it is moderated by familial risk for depression. The association between sadness and the FN in the current sample was stronger among high-risk adolescents, who had a parent with a history of depression, compared to low-risk adolescents, even after adjusting for differences in neuroticism. In other words, among high-risk adolescents the magnitude of the FN was more variable and was strongly modulated by current mood state; among low-risk adolescents the FN was relatively invariable was only weakly (and non-significantly) modulated by mood.

Additionally, high-risk adolescents in the current sample reacted more strongly to the negative mood induction, even though no group differences in mood were present at baseline, an effect which was explained in part due to individual differences in trait neuroticism. An elevated level of neuroticism has been shown to be a risk factor for depression (Duggan et al. 1995; Kendler et al. 2004) and to predict susceptibility to negative mood inductions (Larsen and Ketelaar 1989). As expected, the high-risk adolescents in the current study reported higher levels of neuroticism, and across the whole sample neuroticism predicted both baseline sadness as well as reactivity to the mood induction. However, risk status also uniquely predicted reactivity to the mood induction beyond the effect of neuroticism, indicating that these were independent, additive effects—and only risk status subsequently moderated the sadness-FN link. The moderating role of risk status on the association between negative affect and the FN, therefore, does not appear to be a direct result of neuroticism, but rather reflects a distinct

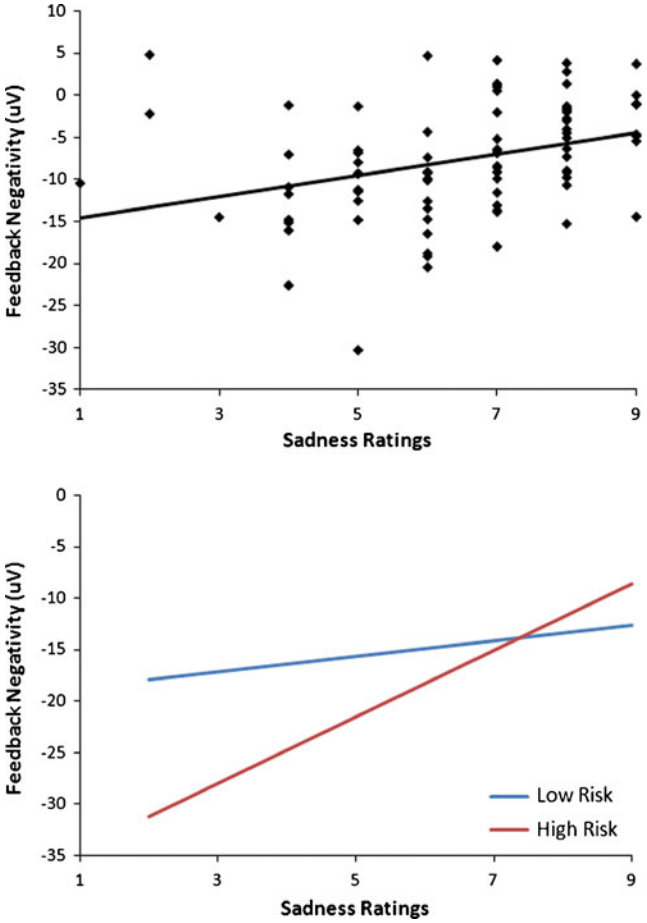

Fig. 4 Top: Scatterplot depicting the relationship between post-induction sadness and the feedback negativity (loss minus gain) in the overall sample. Bottom: Regression lines depicting the relationship separately for low- and high-risk adolescents, after removing the two outlying participants (with sadness ratings un-centered for display purposes only). It should be noted that, after removing the two outliers, there were no high-risk adolescents reporting a low level of post-induction sadness (<4)

mechanism of depression vulnerability: an information processing abnormality that operates in addition to the risk conveyed by elevated neuroticism. This pattern suggests a pathway in which adolescents at increased risk for depression are characterized by greater reactivity to negative stimuli (i.e., sad mood induction), which then acts to alter subsequent information processing by blunting neural responses to monetary gains and losses. While the negative stimulus used here was a sad mood induction, it will be of interest to see whether the observed results are specific to sadness or generalize to negative contexts more broadly. In contrast to the mood induction results reported here, Joormann and colleagues (2007) examined information processing biases among high-risk girls and did not find any association between risk status and reactivity to their negative mood induction. Their sample was pre- and early-adolescent (aged 9–14), however, whereas the current sample was older (aged 15–17). Adolescence is generally a period of heightened emotional reactivity (Arnett 1999), and as such it stands to reason that differences in emotional reactivity between high- and low-risk girls may emerge only during middle or late adolescence. That is, the association between risk status and reactivity to emotional stimuli may interact with age, a possibility that warrants future study.

In a recent commentary on the literature examining deficient reward processing in depression, Forbes (2009) emphasized the importance of shifting toward a developmental perspective in order to better understand how early abnormalities may predict the onset and course of illness. In this regard, one strength of the current study is that none of the adolescents themselves had any history of a major depressive episode, thereby minimizing the possibility that FN magnitude was influenced by enduring effects of past depressive illness. This will allow us to examine the extent to which risk status, reactivity to the mood induction, and subsequent FN magnitude may be combined in predicting the onset of a future depressive episode in the current sample, a direction that we are presently pursuing. Insofar as lifetime depression was assessed retrospectively here, shifting to a prospective study design will also reduce the influence of recall bias which is inherent in any retrospective design.

The gambling task employed in the current study rewarded response choices on exactly 50% of the trials, and no true learning was possible. One limitation of this approach is that abnormal response styles associated with depression vulnerability could not be examined. Accordingly, it may be fruitful for future studies to examine the FN in a context where it may be used to predict behavior and learning during the laboratory task. For example, Pizzagalli and colleagues (2005) have developed a signal-detection paradigm in which specific stimuli are differentially reinforced, thereby allowing for an objective measure of how rewards impact response styles. On this task, depressed adults exhibit impaired integration of reinforcement patterns into their behavior over time (Pizzagalli et al. 2008). Similarly, Forbes and colleagues (2007) have used a gambling task that varies both reward probability and magnitude across trials to identify response style abnormalities among young adolescents with major depression. By incorporating the FN into tasks such as these, it may be possible to examine the extent to which information processing abnormalities, as indicated by FN magnitude, predict behavioral responses to gains and losses associated with depression.

It is worth noting that, although the association between state mood and the FN was significantly stronger among high-risk adolescents, FN magnitude was reduced in the high-risk group compared to the low-risk group only at the highest levels of measured sadness—and the main effect of risk was non-significant. This pattern predicts that group

differences between low- and high-risk adolescents may continue to become more pronounced in response to more extreme disturbances in mood, or in response to major life stressors that exert a greater impact than laboratory-based negative inductions. Conversely, at low levels of sadness the high-risk group actually exhibited an increased (albeit non-signifcant) FN compared to the low-risk group. This group difference at lower levels of sadness must be interpreted with caution, however, due to the restricted range of post-induction sadness ratings. High-risk adolescents were more sensitive to the negative mood induction on average, and only a single high-risk adolescent reported a low level of sadness following the sad mood induction; her data was statistically deviant from the rest of the high-risk group. On the other hand, there is evidence that, among individuals at high genetic risk, depression frequently occurs in the absence of major life stressors (Kendler et al. 2001). From this perspective, it is possible that the interaction between risk and state sadness observed here will only be present for relatively mild stressors, and that for more severe stressors state sadness will be closely linked with blunted FN magnitude for all individuals, regardless of risk status. In the current study, all participants received the sad mood induction, making it difficult to draw strong conclusions about the relationship between the FN and risk status at relatively neutral moods. To clarify this, it may be of interest to examine the link between risk status and the FN under different conditions. In one recent study, we compared the sad mood induction used here to a neutral mood induction among an unselected sample (Foti and Hajcak 2010). State sadness was significantly higher in the sad mood condition, and the FN was inversely related to state sadness, but FN magnitude was not directly predicted by the assigned condition. That is, the FN was reduced among individuals who became sadder, regardless of which induction they received. A stronger manipulation, then, may be to use a positive mood induction as a comparison condition.

The results of the current study are qualified by several other limitations. Only female adolescents were included in the study, so it remains to be shown the extent to which these results generalize to males. Another limitation is that both maternal and paternal depression were assessed primarily through the report of the mother, as opposed to interviewing both parents. We note, however, that spouses are generally accurate informants of lifetime depression compared to direct interviews (Mendlewicz et al. 1975), and while the negative predictive power of family history reports is only moderate, positive predictive power is high (Cohen 1988). Although the majority of participating families had a history of maternal depression, in future studies it may be of interest to examine both maternal and paternal depression separately to examine the extent to which these convey independent risk mechanisms (Klein et al. 2005). It may also be of interest to examine depression history among other family members, such as siblings and grandparents (Weissman et al. 2005), to establish a more comprehensive risk criterion and more fully separate adolescents at high and low risk for depression. Lastly, the FN was only measured here after the mood induction occurred, leaving open the possibility of reverse causation: baseline differences in FN amplitude may predict reactivity to the mood induction. This should be addressed in future studies using a repeated-measures design.

By recording ERPs during a gambling task in adolescents either with or without a parental history of major depression, the current study begins to bridge the existing literatures on depression vulnerability, reward sensitivity, and the FN. Specifically, it appears that the magnitude of the FN is strongly influenced by state sadness in adolescents at increased risk for depression, whereas among adolescents at low risk the FN is only weakly influenced by state sadness. This influence of risk status appears to be independent of neuroticism, which is also increased among high-risk adolescents and predicts negative mood reactivity. Only risk status, however, moderates the relationship between state sadness and FN magnitude. These results indicate that the FN is a useful neural measure for detecting abnormal reward sensitivity in high-risk populations and, by examining the FN in conjunction with family history and personality characteristics, it may be possible to attain a better understanding of the mechanisms of depression vulnerability.

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