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Blunted neural response to rewards prospectively predicts depression in adolescent girls

JENNIFER N. BRESS,[a] DAN FOTI,[a] ROMAN KOTOV,[b] DANIEL N. KLEIN,[a] AND GREG HAJCAK[a]

[a]Department of Psychology, Stony Brook University, Stony Brook, New York, USA
[b]Department of Psychiatry and Behavioral Sciences, Stony Brook University, Stony Brook, New York, USA

Abstract

The prevalence of depression increases substantially during adolescence. Several predictors of major depressive disorder have been established, but their predictive power is limited. In the current study, the feedback negativity (FN), an event-related potential component elicited by feedback indicating monetary gain versus loss, was recorded in 68 never-depressed adolescent girls. Over the following 2 years, 24% of participants developed a major depressive episode (MDE); illness onset was predicted by blunted FN at initial evaluation. Lower FN amplitude predicted more depressive symptoms during the follow-up period, even after controlling for neuroticism and depressive symptoms at baseline. This is the first prospective study to demonstrate a link between a neural measure of reward sensitivity and the first onset of an MDE. The current results suggest that low reward sensitivity may be an important factor in the development of depression.

Descriptors: Reward, Depression, Feedback negativity, Feedback-related negativity, Predictors

Adolescence is a time of heightened risk for depression onset. Point prevalence (i.e., prevalence of current depression at a given age) increases after age 12, and cumulative prevalence (i.e., the percentage of children who have developed depression at any point in their lives) reaches 10% by age 16 (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003). Gender differences in rates of depression also emerge during midpuberty (Angold, Costello, & Worthman, 1998), with significantly more girls developing depression than boys, particularly between ages 15 and 18 (Hankin et al., 1998). Moreover, postpubertal onset of depression is associated with greater risk for recurrence in adulthood compared to prepubertal onset (Rutter, Kim-Cohen, & Maughan, 2006), and pre-adult onset is associated with greater rates of hospitalization, comorbidity, and suicidality than onset in adulthood (Klein et al., 1999; Zisook et al., 2004). Collectively, the existing research suggests that depression in adolescence has a lasting impact—and it is therefore particularly important to identify variables that predict the onset of the disorder during this sensitive time period.

Several predictors of first-onset depression have been established. In addition to prior depressive symptoms (Pine, Cohen, Cohen, & Brook, 1999), parental history of depression is also a robust predictor of depression onset and functional impairment (Goodman, 2007). Furthermore, higher levels of neuroticism are associated with a greater risk of later depression (Kendler, Gatz, Gardner, & Pedersen, 2006). Among women, prior depression, neuroticism, and family history rank among the strongest known predictors of major depression (Kendler, Gardner, & Prescott, 2002; Kendler, Kessler, Neale, Heath, & Eaves, 1993). However, the knowledge of risk factors for depression is incomplete. Indeed, the best fitting predictive model of depression proposed by Kendler and colleagues (1993, 2002) leaves about 50% of the variance unaccounted for. This model includes a comprehensive collection of psychosocial variables, but less attention is given to cognitive or biological variables.

Accumulating behavioral and neurobiological evidence points to low reward sensitivity as a possible risk factor and marker of depression. In contrast to the behavior of healthy individuals, the behavior of depressed adults (Henriques & Davidson, 2000) and children (Forbes, Shaw, & Dahl, 2007) is less modulated by rewards. In a verbal memory task, for instance, healthy adults tend to adopt a more liberal response bias when given the chance to earn money for correct responses as compared to a nonrewarded condition; depressed adults do not show the same difference in response bias (Henriques & Davidson, 2000). Similarly, in a reward-contingent decision task, healthy 10- to 11-year-old boys tend to respond preferentially to high-magnitude reward options compared to low-magnitude reward options when the probability of receiving the reward is high; boys with depression do not (Forbes et al., 2007).

Consistent with behavioral findings, neuroimaging studies indicate that depression is associated with abnormal processing of rewards. Depressed adults show reduced function in a number of reward-related brain areas, particularly the mesocorticolimbic dopamine system; specifically, caudate and ventral striatum

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Address correspondence to: Greg Hajcak, Department of Psychology, Stony Brook University, Stony Brook, NY 11794-2500, USA. E-mail: greg.hajcak@stonybrook.edu

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activity in response to feedback indicating the receipt of a reward is reduced in major depressive disorder (MDD; Pizzagalli et al., 2009; Steele, Kumar, & Ebmeier, 2007). There is similar evidence for hypoactive reward-related brain activity among depressed adolescents (Forbes et al., 2006). It is hypothesized that these areas may specifically relate to the anhedonia that often characterizes depression, and initial investigations suggest that when the reward circuit is activated with deep brain stimulation in adults, anhedonic symptoms can be reduced (Schlaepfer et al., 2008).

Although there is consistent behavioral and neurobiological evidence of low reward sensitivity in *current* depression, relatively few studies have investigated whether abnormal reward processing also relates to increased *risk* for developing depression, especially in youth. Two studies to date have suggested that risk for depression is associated with decreased responsiveness to reward in children and adolescents. One study found that less risky decision making about reward in 11-year-old boys predicted internalizing disorders at age 12 (Forbes et al., 2007). Another study found that never-depressed 10- to 14-year-old girls with depressed mothers showed abnormalities in reward-related brain activation when anticipating rewards (Gotlib et al., 2010). Although the latter study did not demonstrate a direct relationship between reward response and first onset of depression, the association between abnormal reward-related brain activation and parental history—a known predictor of depression—is consistent with the possibility of such a relationship.

In addition to functional magnetic resonance imaging (fMRI) studies, recent work has begun to assess neural sensitivity to rewards using the feedback negativity (FN), a frontocentral event-related potential (ERP) component that differentiates feedback indicating monetary gain versus loss. Insofar as the difference between response to gain and loss is maximal approximately 300 ms following feedback, the FN reflects a relatively early neural measure of reward sensitivity. Existing psychophysiological studies have found that higher depressive symptom and state sadness scores are associated with a smaller magnitude of the FN (Foti & Hajcak, 2009, 2010). These results are similar to those found in the affective bias literature, wherein people with depression do not show the increased neural bias toward positive affective stimuli (e.g., happy faces) seen in their healthy peers (Deldin, Keller, Gergen, & Miller, 2001) and exhibit reduced activity to positive compared to negative words (Shestyuk, Deldin, Brand, & Deveney, 2005). Given the well-documented association between current depression and abnormal reward processing, the FN has the potential to be a risk factor for later depression; however, there are no studies to date investigating this association prospectively. Building upon the preliminary evidence (Foti & Hajcak, 2009, 2010), we sought to test whether blunted neural response to rewards versus nonrewards (i.e., the FN) prospectively predicts the first onset of major depressive episodes (MDEs) and later depressive symptoms among female adolescents.

Our group previously conducted a study in which we recorded the FN among never-depressed 15- to 17-year-old adolescent girls oversampled for parental history of MDEs (Foti, Kotov, Klein, & Hajcak, 2011). Prior to completing the FN task, participants were given a sad mood induction to prime depressogenic biases. Within the group with a parental history of MDEs, but not the group without a parental history, induced sadness strongly predicted a blunted FN. These results, together with those of Gotlib and colleagues (2010), suggest that girls at risk for depression show neurophysiological differences in the way they process reward.

The current study is a follow-up of our never-depressed cohort. We interviewed the same participants nearly 2 years after their initial visit in order to determine whether blunted FN amplitude at baseline would predict first MDE and severity of depressive symptoms during the follow-up.

Methods

Initial Assessment

We recruited eighty-four 15- to 17-year-old female adolescents who had never had an MDE (Foti, Kotov, et al., 2011). They were oversampled for parental history of MDEs, so that 38 had a biological parent with lifetime MDEs. Participants were recruited by contacting a random sample from a commercial mailing list of households with girls in the targeted age range. Adolescents were interviewed to determine whether they had ever experienced an MDE and would therefore be ineligible. An additional interview was conducted with the adolescent's biological mother (or her father, in four cases) to assess lifetime history of MDEs for both herself and the coparent. There were 22 participants with depressed mothers, 10 with depressed fathers, and 6 whose parents were both depressed. The mood module of the Patient Health Questionnaire (PHQ-9; Kroenke, Spitzer, & Williams, 2001) was used in both adolescent and mother interviews to evaluate current and past depressive episodes. The PHQ-9 assesses nine symptoms on a 0–3 scale; responders are diagnosed with an MDE if at least five items—including anhedonia or depressed mood—are rated 2 or 3. The PHQ-9 has a sensitivity of .77 and a specificity of .94 (Wittkampf, Naeije, Schene, Huyser, & van Weert, 2007) and corresponds well with the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV) in assessment of lifetime depression (Cannon et al., 2007).

At the initial testing session, participants completed the General Depression scale of the Inventory of Depression and Anxiety Symptoms (IDAS; Watson et al., 2007) to assess depressive symptoms within a 2-week period prior to the assessment; the IDAS was chosen for this purpose because the PHQ-9 is optimized to detect MDEs, whereas the IDAS is optimized to measure depression severity. The Big Five Inventory (BFI; John & Srivastava, 1999) was used to assess neuroticism.

Participants were given a sad mood induction and completed two laboratory tasks; they were then given another sad mood induction and completed another two laboratory tasks. Mood inductions consisted of 5-min video clips from the movies *The Champ* and *My Girl*. The video clips were followed by music from Gabriel Faure's *Piano Quintet No. 1 in D Minor (Op. 89)*, a melancholy classical piece on strings and piano, played in the background during all tasks. Task order was randomized across participants.

The current study focuses on neural correlates of reward, measured during a computerized guessing task that consisted of 40 trials. On each trial, participants were asked to choose one of two doors shown side by side on a computer monitor; the graphic remained visible until a choice was made. A fixation mark then appeared for 1000 ms, followed by feedback screen for 2000 ms. Feedback consisted of either a green "↑", indicating a gain of \$0.50, or a red "↓", indicating a loss of \$0.25; these amounts were chosen to give gains and losses equivalent subjective values (Tversky & Kahneman, 1992). After the feedback, a fixation mark was presented for 1500 ms, followed by a screen reading "Click for the next round," which remained onscreen until participants responded. Participants received 20 trials each of gain and loss feedback, presented in a random order.

Participants rated their moods on a 9-point scale (1 = *maximally happy*, 9 = *maximally sad*) before and after each film clip and at the end of the study session. Because the mood rating was conceptualized as a quantification of sadness, this scoring was used so that a greater degree of sadness would translate into a higher score. Mood was measured as a difference score between the first rating and the postinduction rating before the guessing task.

Participants gave written assent, and their parents gave written informed consent, for their participation. This study was formally approved by the Stony Brook University Institutional Review Board.

Follow-up Assessment

Of the original 84 participants, 68 were interviewed over the phone between 19 and 23 months ($M = 21$ months) after the initial laboratory visit. Thus, 81.0% of the cohort completed the follow-up; 4.7% could not be traced, and 14.3% declined to participate. At the follow-up, participants had attained a mean age of 17.76 years ($SD = 0.88$). No significant differences in age, ethnicity, parental history, depression, neuroticism, mood change, or FN were found between those who participated in the follow-up and those who did not (all p values > .05).

The primary measure collected at follow-up was the diagnosis of an MDE during the interval since the initial assessment. Because participants had no history of MDEs at the initial evaluation, this diagnosis indicates the first episode of major depression. A dichotomous MDE diagnosis and a continuous measure of depression severity were obtained using the depression module of the Diagnostic Interview Schedule for Children (DISC; Costello, Edelbrock, & Costello, 1985; Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000). The DISC is a structured diagnostic interview that assesses DSM-IV and International Classification of Diseases, 10th Revision (ICD-10) criteria. It consists of a number of "stem" questions to screen for possible symptoms and follows up positive responses with "contingent" questions to assess whether each symptom meets criteria. The standard depression module of the DISC includes 22 items assessing different aspects of DSM-IV and ICD-10 major depression symptoms. The DISC was modified for the current study to remove two of three questions related to suicidality, as the Institutional Review Board determined them to be inappropriate for telephone interviews. The question about recurrent thoughts of death was retained, resulting in 20 questions altogether. Participants were diagnosed with an MDE if they had met five or more of the nine DSM-IV criteria—including low mood or anhedonia—for at least 2 weeks since the initial assessment and had experienced clinically significant impairment. Test–retest reliability of MDD diagnosis with the DISC-IV in clinical samples is good to very good, with a κ of .92 for youth self-reports (Shaffer et al., 2000). In addition to being used to diagnose MDEs, the DISC provides dimensional assessment of maximal depression severity during the interval, measured as the number of items endorsed (maximum of 20 on the version used).

Psychophysiological Recording and Data Reduction

Recordings were collected during the guessing task with a 34-channel custom cap (Cortech Solutions, Wilmington, NC) arranged according to the 10/20 system, using the ActiveTwo BioSemi system (BioSemi, Amsterdam, Netherlands). The signal was pre-amplified with a gain of 1 and 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 104 Hz.

Electroencephalogram (EEG) was epoched into feedback-locked segments beginning 200 ms before and ending 800 ms after the onset of feedback presentation. The FN was scored as the mean amplitude from 250 to 350 ms after feedback presentation at a pooling of Fz and FCz electrode sites. Analyses were limited to the Fz and FCz sites because the amplitude difference between gain and loss trials is maximal at these locations (Foti, Kotov, et al., 2011). We examined the difference between gains and losses as well as the mean amplitudes on gain and loss trials separately. The latter might be important insofar as recent work has highlighted the importance of being able to evaluate responses to gains and losses separately (Bernat, Nelson, Steele, Gehring, & Patrick, 2011; Foti, Weinberg, Dien, & Hajcak, 2011); namely, it appears that the responses to gains and losses represent two separate processes contributing to the difference-wave FN, which may relate differently to the symptoms of depression.

Artifact due to eyeblinks was corrected using the method from Gratton, Coles, and Donchin (1983), and specific channels were removed from individual trials using both visual inspection and a semiautomated procedure that rejected channels with a voltage step of more than 50 μV between sample points, a within-trial voltage difference of more than 300 μV, or a voltage difference of less than 0.5 μV in a given 100-ms interval. BrainVision Analyzer (Brain Products, Munich, Germany) was used for off-line EEG analysis.

Results

Predicting Major Depressive Episodes

Characteristics of the current participants at initial assessment are presented in Table 1; also included are test statistics for comparisons between those who later experienced MDEs and those who did not. Of the 68 participants evaluated at follow-up, 16 (24%) had experienced an MDE since the initial evaluation. MDE diagnosis was not significantly predicted by parental history of MDEs. Participants with an MDE at follow-up had significantly higher depressive symptom scores on the IDAS at baseline (Cohen's $d = .59$), and they showed marginally significant greater reactivity to the mood induction at baseline. No significant group differences were observed for parental history or neuroticism (ps > .05).

The FN at initial assessment was observed as a frontally maximal ERP component peaking at approximately 300 ms; consistent with the literature, the response to losses was significantly less positive than the response to gains, $t(67) = -6.64$, $p < .001$ (losses: $M = 11.30$ μV, $SD = 9.30$ μV; gains: $M = 16.36$ μV, $SD = 9.83$ μV). The FN in response to loss correlated with baseline neuroticism ($r = .25$, $p < .05$) but the response to gain did not ($r = .09$, $p = .44$), indicating a blunted neural response specifically to loss in participants with higher neuroticism scores. The difference between these correlations was significant, $t(65) = 2.09$, $p < .05$. Independent-samples t tests were used to compare the FN in the groups with and without MDEs over the follow-up period. Considering the FN as a difference score (i.e., losses minus gains), the group with MDEs had a smaller FN at initial evaluation than the group without (Cohen's $d = .50$). Figure 1 shows the topographical layout of the FN and feedback-locked ERPs for participants who later developed an MDE (bottom) and for participants who did not (top). These two groups did not differ significantly when the FN was measured in response to gains (Cohen's $d = .30$) or losses (Cohen's $d = .01$) alone.

Table 1. *Characteristics of Participants*

	MDE diagnosis since initial assessment				
	No MDE		MDE		
	($n = 52$)		($n = 16$)		
Variables at initial assessment	*n*	%	*n*	%	Test statistic
Parental history					
No major depressive episodes	29	78.4	8	21.6	$\chi^2(1) = .16$
One or more major depressive episodes	23	74.2	8	25.8	
Ethnicity					
Caucasian	48	76.2	15	23.8	$\chi^2(1) = .04$
Other	4	80.0	1	20.0	
	M	*SD*	*M*	*SD*	
Age at follow-up (years)	17.81	.89	17.63	.89	$t(66) = 0.65$
Neuroticism (BFI)	23.50	5.72	24.00	8.19	$t(66) = -0.28$
Change in mood after induction	3.19	1.82	4.06	1.73	$t(66) = -1.69^{\dagger}$
Depressive symptoms (IDAS)	35.06	8.40	41.75	13.21	$t(66) = -2.41$*
Feedback negativity (μV)					
Loss	11.26	9.67	11.43	8.26	$t(66) = -0.06$
Gain	17.16	9.84	13.75	9.63	$t(66) = 1.22$
Loss – gain	–5.90	6.52	–2.32	4.64	$t(66) = -2.04$*

Note. IDAS = Inventory of Depression and Anxiety Symptoms; BFI = Big Five Inventory.
*Group difference significant at $p < .05$. †Group difference marginally significant, $p < .10$.

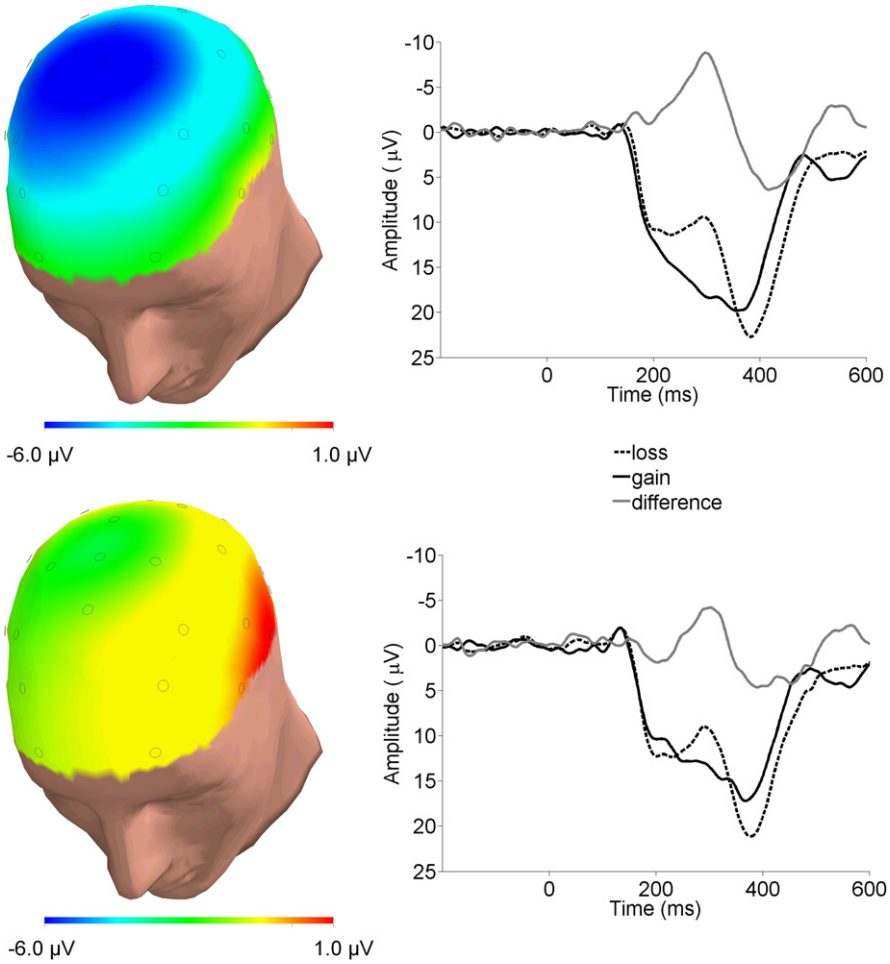

Figure 1. Left: Scalp distribution of the difference between losses and gains from 250 to 350 ms after feedback presentation. Right: feedback-locked ERPs at a pooling of Fz and FCz electrodes in response to losses and gains, as well as the loss–gain difference. Results are shown for participants who did not later develop an MDE (top) and for participants who did (bottom). Negative values are plotted up.

Table 2. *Correlations between Baseline Measures and Later Depression*

		Baseline measures						
	Interval depression	Depression (IDAS)	Neuroticism (BFI)	Parental history	Mood reactivity	FN—gains	FN—losses	FN—difference
Interval depression		.38**	.30*	.15	.14	−.26*	−.12	.22
Baseline measures								
Depression (IDAS)			.66**	.10	.24*	−.04	.12	.23
Neuroticism (BFI)				.23	.18	.09	.25*	.22
Parental history					.31*	−.05	.01	.09
Mood reactivity						−.27*	−.06	.32**
FN—gains							.79**	−.40**
FN—losses								.25*
FN—difference								

Note. Interval Depression = depression severity during the worst 2 weeks since baseline; FN = feedback negativity; IDAS = Inventory of Depression and Anxiety Symptoms; BFI = Big Five Inventory.
*Significant at $p < .05$; **significant at $p < .01$.

Predicting Depression Severity

Depression severity during the worst point of follow-up had approximately normal distribution, with a mean of 10.0 and standard deviation of 4.4. It was predicted by depressive symptoms on the IDAS ($r = .38$, $p < .01$) and neuroticism on the BFI ($r = .30$, $p < .05$) at initial evaluation, but not by parental history of MDEs ($r = .15$, $p = .25$) or reactivity to the mood induction ($r = .14$, $p = .29$).

Correlations between baseline measures and later depression are reported in Table 2, and the relationship between depression and FN in response to gain is illustrated in Figure 2. With regard to the FN, a trend was observed for the loss–gain difference ($r = .22$, $p = .08$) such that greater future depression severity was predicted by a smaller differentiation between gains and losses at the initial assessment. Depression severity was significantly predicted by the ERP response to gain ($r = -.26$, $p < .05$), but not to loss ($r = -.12$, $p = .33$); the difference between the correlation with gain and the correlation with loss was marginally significant, $t(65) = 1.82$, $p = .07$. These correlations indicate that participants with higher symptom scores had a blunted neural response to gain, in particular.

To test whether FN amplitude has unique predictive power, we adjusted for other significant predictors using multiple regression. When controlling for baseline depression and neuroticism, the FN in response to gain uniquely and significantly predicted later continuous depression score, $R^2 = .21$, $F(3,60) = 5.46$, $p < .01$; $\beta = -.26$, $t(60) = -2.22$, $p < .05$, semipartial $r = -.25$; the contribution of baseline depression was marginally significant, $\beta = .27$, $t(60) = 1.78$, $p = .08$, semipartial $r = .20$; and the contribution of baseline neuroticism was not significant, $\beta = .15$, $t(60) = 0.94$, $p = .35$, semipartial $r = .11$. None of the predictors were uniquely significant when FN was measured as the response to losses, $R^2 = .19$, $F(3,60) = 4.55$, $p < .01$; FN: $\beta = -.19$, $t(60) = -1.61$, $p = .11$, semipartial $r = -.19$; baseline depression: $\beta = .30$, $t(60) = 1.96$, $p = .06$, semipartial $r = .23$; baseline neuroticism: $\beta = .15$, $t(60) = 0.94$, $p = .35$, semipartial $r = .11$, or as the loss–gain difference ($R^2 = .17$, $F(3,60) = 4.00$, $p < .05$; FN: $\beta = .13$, $t(60) = 1.10$, $p = .28$, semipartial $r = .13$; baseline depression: $\beta = .30$, $t(60) = 1.90$, $p = .06$, semipartial $r = 22$; baseline neuroticism: $\beta = .07$, $t(60) = 0.47$, $p = .64$, semipartial $r = .06$. However, for both analyses, the contribution of baseline depression was marginally significant.

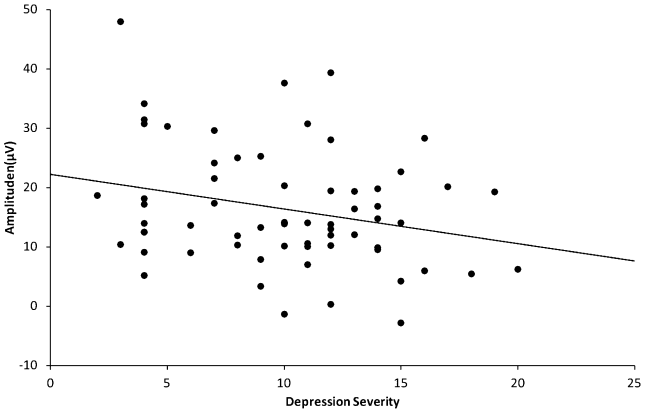

Figure 2. Scatter plot illustrating the relationship between interval depression severity and the FN in response to gains.

Discussion

This is the first prospective study to demonstrate that deficits in neural processing of rewards predict the onset of MDEs and the severity of future depressive symptoms. Never-depressed adolescent girls who experienced an MDE over the 21-month follow-up had shown a blunted FN at initial evaluation (measured as a difference score) compared to girls who did not develop an MDE. That is, reduced neural sensitivity to rewards versus losses predicted the subsequent onset of first-episode depression. When depression was considered dimensionally, a reduced ERP response to gains in particular predicted maximal severity of depressive symptoms in the follow-up period. Unlike studies of depression recurrence, the present investigation analyzed first onset, showing that the blunted FN *precedes* the MDE and is not a result of past depressive episodes. The current findings extend the results of previous studies, which have found decreased responsiveness to reward associated with current depressive symptoms (Forbes et al., 2006; Henriques & Davidson, 2000; Pizzagalli et al., 2009; Steele et al., 2007) and with family history of depression (Gotlib et al., 2010).

Also consistent with the literature (Fergusson, Horwood, Ridder, & Beautrais, 2005; Klein, Shankman, Lewinsohn, & Seeley, 2009; Pine et al., 1999; Rutter et al., 2006), baseline sub-

clinical depression symptom severity predicted severity of later depression, such that the never-depressed girls with a greater number of depressive symptoms at baseline had more severe depressive symptoms during the follow-up; higher neuroticism at baseline likewise predicted more severe depressive symptoms later. However, the FN in response to gains predicted a small but significant portion of the variance even when holding the other sources of variance constant. The effect sizes of the relationship between FN and both the dichotomous and continuous measures of depression were comparable to the effect sizes for baseline depressive symptoms and neuroticism, suggesting that the FN may account for as much variability in depression outcomes as these well-established predictors.

Unexpectedly, parental history of MDEs did not predict depressive symptoms or diagnosis. This was likely because of a lack of power; the sample may have been too small to detect a difference between the high- and low-risk groups. Another possibility is that by excluding participants who had already experienced a depressive episode by age 15, we may have excluded those who would have shown the expected association between family history and depression (Hammen, Brennan, & Keenan-Miller, 2008; Weissman et al., 1987).

The unique contribution of the FN to the continuous index of later depression was significant only in response to gain, although the effect for loss–gain differences was marginally significant. These results are consistent with findings that the FN is primarily a reflection of response to reward rather than to loss (Foti, Weinberg, et al., 2011; Holroyd, Pakzad-Vaezi, & Krigolson, 2008). For instance, Carlson, Foti, Mujica-Parodi, Harmon-Jones, and Hajcak (2011) used both ERP and fMRI measures to examine reward responsiveness in the same subjects. Principal components analysis suggested that variation in the gain minus loss difference waveform reflects a positive deflection in the EEG in response to rewards that was absent on nonrewards (also see Foti, Weinberg, et al., 2011). Moreover, this component was correlated with BOLD activation in reward-related mesocorticolimbic brain areas, including the ventral striatum and the caudate; these areas are known to be associated with reward processing and to show reduced functioning in depression (Forbes et al., 2006; Pizzagalli et al., 2009; Steele et al., 2007).

The results of the current study suggest that low reward responsiveness, as represented by a blunted FN, may be an important factor in the development of depression. Existing models describe depression as a multifactorial disorder with multiple etiological pathways (Kendler et al., 2002); particularly relevant is the internalizing pathway comprising factors including genetic risk, neuroticism, and past depression. However, the model proposed by Kendler and colleagues only accounts for 52% of variance, and one explanation they offer is that the model does not comprehensively assess the cognitive components of risk. In the current study, the predictive power of the FN was separate from the effects of neuroticism and depressive symptoms, indicating a distinct role for low reward responsiveness. Thus, decreased neural responsiveness to reward, and subsequent or concurrent anhedonia, may be an extra step in the internalizing pathway or may be part of an additional etiological pathway.

It remains to be determined whether the blunted FN is trait-like, developing early in life and remaining consistent regardless of current depressive status, or whether the appearance of the blunted FN is an early symptom of depression that is detectable before self-reported depressive symptoms. Additional research will also need to investigate whether the decreased FN seen before the onset of depression is associated with a behavioral decrease in reward responsiveness or whether it precedes the behavioral effects.

Moreover, it is unclear whether the sad mood manipulation is necessary to elicit FN indicative of depression risk. Although it could be that the predictive aspect of the FN only emerges in the context of a sad mood, the results of the current study could reflect a stable alteration in the processing of rewards that is present in individuals at risk for depression regardless of current mood state. We are currently investigating this question.

Analysis of reward-related electrocortical activity could potentially be used to identify children who may be at risk for developing depression and to implement early intervention programs. Promising work has been done with early intervention for MDD, finding that preventative efforts may reduce rates of first-onset MDD by nearly 25% (Cuijpers, van Straten, Smit, Mihalopoulos, & Beekman, 2008). In universal prevention studies, the number needed to treat (NNT; i.e., the number of patients that would need to be treated to prevent one additional case of MDD, as compared to an untreated group) is 22, which is relatively high, and selective prevention strategies based on known risk factors offer a substantial improvement (NNT = 16; Cuijpers et al., 2008). By exploring additional risk factors such as the FN, NNT could be further improved.

A limitation of the current study is the relatively small sample size; the follow-up sample consisted of 68 participants, and only 16 had developed MDEs. Study retention was excellent, but the original cohort was only moderate in size. A goal of the current study was to investigate a possible link between the FN and later MDEs; now that such a link has been established, additional studies with larger samples are warranted. For the FN to guide preventative treatment, it will be necessary to determine cutoffs with reasonable sensitivity and specificity, which will also require a larger sample. Another limitation is the brief telephone interview used for participant selection, which could have missed some cases of past depression. However, the PHQ-9 shows good agreement with semi-structured interviews (Cannon et al., 2007). Given that the DISC interview assessed MDEs rather than MDD, it also is possible that some of the participants may have had bipolar disorder rather than major depression; this was not evaluated, but given low prevalence of bipolar disorder, it is likely that at most one participant was misclassified. The follow-up was relatively short in duration; thus, there will likely be some new onsets of depression in those participants who did not meet criteria for an MDE by the time of the 21-month follow-up. Further research will be needed to investigate the long-term predictive ability of the FN.

In summary, reduced differentiation between gain and loss predicted a first episode of depression among adolescent girls, and blunted neural responsiveness to gain in particular predicted greater depression severity. This is the first study to show that deficits in reward processing, and particularly neural measures of those deficits, predict first major depressive episodes. Although this research is still in an early phase, the FN could represent an etiological factor not recognized in current models of depression.

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