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Psychiatry Research 134 (2005) 11–25

PSYCHIATRY RESEARCH

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Affect-modulated startle in adults with childhood-onset depression: Relations to bipolar course and number of lifetime depressive episodes

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Received 16 August 2004; received in revised form 3 November 2004; accepted 7 January 2005

Abstract

To study affect regulation in adults with unipolar (n=38) and bipolar (n=38) forms of childhood-onset depression (COD), as compared with adults with no history of psychiatric illness (n=60), we examined affective modulation of the startle eyeblink reflex. Participants were subjected to binaural bursts of white noise while viewing pictures designed to elicit pleasant, neutral, or unpleasant affective states. The blink response was recorded from surface electrodes over the *orbicularis oculi* muscle during and following pictures. Participants rated the valence and arousal of their responses. Unlike control or bipolar groups, the unipolar group displayed a greater startle during the neutral condition than during the pleasant condition, and failed to display an increase in startle during the unpleasant condition. The bipolar group, unlike the unipolar and control groups, displayed a similar startle response after pleasant and unpleasant pictures. Participants with a high number of lifetime depressive episodes displayed a blunted startle response across affective conditions. Groups reported similar subjective responses to affective stimuli. Current affective symptoms and comorbid diagnoses did not influence startle modulation. In unipolar and bipolar forms of COD, unusual affective modulation or maintenance of the startle response, respectively, may reflect underlying deficits in affect regulation.

Keywords: Depression; Bipolar disorder; Affect regulation; Startle reflex; Early onset; Recurrence

1. Introduction

A central goal of research on mood disorders is to understand variants, identify potential subtypes, and thereby reduce phenotypic heterogeneity. Because age at onset is one source of heterogeneity, there has been

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doi:10.1016/j.psychres.2005.01.001

increasing interest in characterizing mood disorders as a function of the stage in the life cycle in which they first occur. Childhood-onset depression (COD) has a comparatively high familial loading of depression (Bland et al., 1986; Kovacs et al., 1997; Kupfer et al., 1989; Moldin et al., 1991; Price et al., 1987; Weissman et al., 1987), and it tends to involve a chronic, severe course and high rates of recurrence (Harrington et al., 1990; Kovacs, 2001; Newman et al., 1996; Weissman et al., 1999). The underlying correlates of course and outcome in COD are not yet characterized, but essential deficits may involve affect regulation. Because the cortical and subcortical regions implicated in affect regulation (see Davidson, 2002) continue to develop through adolescence (Casey et al., 2000; Durston et al., 2001), the experience of childhood mood disorders may be associated with pathways of neural development that play a role in long-term dysfunction or heightened risk for subsequent psychopathology.

One quarter to one half of all individuals with COD develop bipolar illness (Geller et al., 2001; Strober et al., 1993). Thus, an important question is how affect regulation differs in unipolar and bipolar forms of COD. A growing literature in affective neuroscience indicates that abnormalities of affective processing are associated with symptoms of mood disorders (Phillips, 2003) and suggests that the unipolar and bipolar forms of mood disorders involve differences in neural activation during resting and affective states (Baxter et al., 1989; Bench et al., 1992; Biver et al., 1994; Blumberg et al., 1999, 2000; Drevets, 1999; Krüger et al., 2003). For instance, bipolar disorder has been associated with decreased orbital prefrontal cortex (Blumberg et al., 1999) and anterior cingulate activation (Blumberg et al., 2000), whereas major depressive disorder has been associated with the opposite pattern of activation in those regions (Bench et al., 1992; Biver et al., 1994; Liotti et al., 2002). Bipolar disorder has also been associated with changes in affect-relevant regions such as the caudate (Blumberg et al., 2000) and insula (Krüger et al., 2003). Furthermore, some neural abnormalities appear to be present regardless of current mood state and may represent trait-like differences in affect regulation (Blumberg et al., 2003; Liotti et al., 2002). Other physiological indices of affect regulation could also identify markers of unipolar and bipolar COD.

Affect-modulated startle may provide an avenue for characterizing differences in affect regulation in unipolar and bipolar forms of COD. The startle response is a defensive reflex that is reliably elicited by threatening cues and is influenced by the affective context within which it is elicited. It is potentiated (i.e., increased) in the presence of a conditioned fear stimulus (Lang, 1995), and the amygdala, reticular nuclei, and anterior cingulate cortex are implicated in this phenomenon (Lang, 1995; Pissiota et al., 2003). Startle is attenuated in the presence of pleasant stimuli, and lesion studies with rats indicate that the nucleus accumbens appears to be involved in this phenomenon (Koch et al., 1996). In humans, the startle reflex–operationalized as a change in tension in the *orbicularis oculi*, the muscle encircling the eye's orbit–is potentiated during viewing of unpleasant visual stimuli and attenuated during viewing of pleasant stimuli (Lang, 1995; Bradley et al., 1990, 1999; Cuthbert et al., 1998; Vanman et al., 1998; Vrana et al., 1988).

Although modulation of the startle response occurs during affective states, the response also may be influenced by long-term affective traits. Individuals high on traits related to negative affect, such as fearfulness and harm avoidance, exhibit enhanced startle potentiation to unpleasant pictures (Cook et al., 1991; Corr et al., 1995, 1997). Those high on behavioral activation, a trait related to positive affect, exhibit greater inhibition of startle during pleasant pictures (Hawk and Kowmas, 2003). In addition, forms of psychopathology involving chronic affect dysregulation may disrupt the pattern of change in the startle response during acute affective experience. Previous investigations of this question have primarily focused on anxiety disorders and psychopathy (de Jong et al., 1991, 1996; Grillon et al., 1997, 1998; Lang, 1995; Patrick et al., 1993; Vrana et al., 1992). Studies of anxiety have yielded mixed findings (Grillon and Baas, 2003). Animal phobia is associated with greater startle potentiation during viewing of pictures of feared animals, and panic disorder is associated with greater startle in response to threat of shock in young adults (Grillon et al., 1994). Findings have been less consistent across studies of post-traumatic stress disorder, however (Grillon and Baas, 2003). Criminal psychopathy, a disorder characterized by low fearfulness, is accompanied by a lack of startle

potentiation during unpleasant stimuli (Patrick et al., 1993). Thus, high negative affect–in terms of normal individual differences or anxiety–has generally been associated with increased startle potentiation to unpleasant stimuli, while high positive affect has generally been associated with enhanced startle attenuation to pleasant stimuli.

Depression, it has been posited, involves reduced startle attenuation during pleasant affective states and enhanced startle potentiation during unpleasant states. Emotion-theory models conceptualize depression as marked by low activity in appetitive emotional systems and high activity in aversive emotional systems (Clark and Watson, 1991; Depue and Iacono, 1989; Fowles, 1988), and studies of brain electrical activity have provided support for this claim (Henriques and Davidson, 1990, 1991; Miller et al., 2002). However, extant findings on affect-modulated startle in depression are varied. In a nonclinical sample, young adults' self-rated depression was associated with greater startle potentiation during unpleasant imagery (Cook et al., 1991). Among hospitalized adults, depressed patients exhibited potentiation rather than attenuation during pleasant stimuli but did not differ from psychiatric controls during unpleasant stimuli (Allen et al., 1999). Furthermore, the potentiation of startle during pleasant states occurred only in the subgroup of patients with severe depression. As these findings and a recent review of startle findings with psychiatric samples (Grillon and Baas, 2003) point out, a useful strategy in detecting disorder-related differences in affect-modulated startle is to examine subgroups within a disorder.

Despite indications that bipolar disorder involves important abnormalities in affect regulation, bipolar disorder has been somewhat neglected in research on affective response. In addition, no study to date has examined affect-modulated startle in bipolar disorder. Theoretical models of the disorder emphasize the wide variety of affective experience and fluctuations in affective state as core features (Leibenluft et al., 2003), and behavioral findings have suggested that manic patients display a bias toward pleasant stimuli (Murphy et al., 1999). Moreover, bipolar patients appear to experience chronic symptomatic states over time (Judd et al., 2002). Thus, the affective characteristics of bipolar disorder may involve enhanced response during pleasant affective states as well as during unpleasant states.

More recently, the time course of affect-modulated startle has been examined with regard to depression-related characteristics. The startle response following the offset of unpleasant affective stimuli has been proposed as a measure of automatic (rather than effortful) affect regulation (Jackson et al., 2003). Smaller blink magnitude after an unpleasant picture, then, reflects more effective regulation of negative affect. Following unpleasant affective stimuli, adults with higher depressive symptoms exhibit enhanced startle potentiation (Larson and Davidson, 2001), and those with left frontal EEG asymmetry, which is associated with the tendency to experience positive affect, exhibit startle attenuation (Jackson et al., 2003).

As part of a multistudy project examining affect regulation as a central deficit in COD, we tested the hypothesis that unipolar and bipolar COD participants would exhibit dysregulation of the startle response during and following exposure to affective stimuli. We focused on unipolar and bipolar COD subgroups because these subgroups have experienced different ranges of pathological affect and are likely to differ in their neural processing of affective stimuli. Based on the literature on affect-modulated startle in relation to trait affect and affective disorders and on theoretical models of depression, we predicted that unipolar COD would be associated with increased responses to unpleasant stimuli and decreased responses to pleasant stimuli. On a similar basis, we predicted that bipolar COD would be associated with enhanced responses to both unpleasant and pleasant stimuli. Specifically, we predicted that the unipolar group would exhibit startle potentiation during unpleasant contexts and no startle attenuation during pleasant contexts. Based on evidence of sustained response to unpleasant stimuli in depressed adults (Siegle et al., 2002), we also predicted that the unipolar group would exhibit greater startle response following unpleasant contexts. In contrast, we predicted that the bipolar group would exhibit potentiation during unpleasant contexts, attenuation during pleasant contexts, and a similar startle response to controls following unpleasant or pleasant affective contexts. Because impairment in affect regulation may vary with repeated experience of depression, we postulated

that greater depression recurrence would be associated with enhanced sensitivity to unpleasant stimuli and reduced sensitivity to pleasant stimuli. Thus, we predicted that low frequency of lifetime depressive episodes would be associated with a pattern of startle responding similar to that of controls, whereas a high frequency of lifetime depressive episodes would be associated with enhanced startle responding during unpleasant contexts and decreased startle responding during pleasant contexts.

2. Methods

2.1. Participants

Participants were adults with a history of COD (n=76) and adults with no history of psychopathology (n=60), a subsample from a larger, multidisciplinary research program on childhood-onset mood disorders. All participants provided written informed consent after hearing a complete description of the study, and none had previous experience with the startle paradigm.

COD probands were recruited through prior research studies or community advertisements. Twenty COD probands had participated in a longitudinal, naturalistic follow-up study of COD and had undergone multiple psychiatric assessments over the course of up to 20 years. The other 56 COD probands had been participants during their youth in other studies of shorter durations, including studies of juvenile anxiety disorder, adolescent depression and suicide, and conduct and associated disorders. All probands had extensive clinical or research records supporting the presence of operational DSM-III, DSM-III-R, or DSM-IV diagnoses (American Psychiatric Association, 1980, 1987, 1994) of either depression (major depressive and/or dysthymic disorder) by age 14, or bipolar spectrum disorder (bipolar I, bipolar II, or cyclothymic disorder) by age 17. The mean age at onset of first affective episode was 10.2 years (SD=2.7) for the unipolar group and 12.7 years (SD=3.0) for the bipolar group. In the COD group, 68.4% (76.3% of the unipolars) had a lifetime history of anxiety disorder, and 12.3% (5.6% of the unipolars) had a diagnosis of antisocial personality disorder. The COD bipolar group was no more likely to have had an anxiety disorder or an antisocial personality disorder than was the COD unipolar group (χ^2=3.01 and 3.02, respectively, Ps>0.05).

Control participants were recruited through various avenues, including a marketing directory, a neighborhood program, and previous research studies. Controls received standardized psychiatric evaluations and were included if they had no lifetime history of major psychiatric illness. We excluded an additional four control participants who had elevated depressive symptoms at the time of the physiological assessment.

The groups were comparable in gender (64% female in the COD group, 67% female in the control group) and ethnicity (12% African-American, 83% European-American, and 4% other in the COD group; 18% African-American, 78% European-American, and 3% other in the control group). COD participants were slightly younger than were control participants [M=24.7 years, SD=4.0 and M=26.0 years, SD=4.7, respectively; $F(1,134)=14.73$, $P<0.001$]. The results below did not differ when age was included as a covariate, however. Eleven COD participants were taking antidepressant medication, and the results reported below did not differ when data analyses were conducted without these participants. COD participants were more likely to smoke cigarettes [53% in COD group, 22% in control group; $\chi^2(1, N=136)=13.52$, $P<0.001$] or use marijuana [13% in COD group, 3% in control group; $\chi^2(1, N=136)=4.02$, $P<0.05$] than were control participants. COD and control groups did not differ in their self-reported caffeine consumption, use of alcohol, use of other illicit drugs, or alertness during the assessment.

2.2. Psychiatric diagnoses and symptom ratings

Information about lifetime psychiatric history was obtained in several ways. For probands who had participated in a longitudinal study of COD (Kovacs et al., 1984), diagnoses were available through repeated assessments via the semi-structured Interview Schedule for Children and Adolescents (ISCA) and the Follow-up Interview Schedule for Adults (FISA), using the proband and a parent, or other adult, as informants (Sherrill and Kovacs, 2000). The operational DSM-based diagnoses were subjected to repeated consensus reviews by experienced diagnosticians (Kovacs et al., 1994, 2003). All other participants were assessed using the Structured Clinical

Interview for DSM-IV Patient Version (SCID-I/P) adapted to include childhood diagnoses (First et al., 1995). Each SCID assessment was conducted by an experienced research clinician and included a separate interview with a second informant and a review of supporting clinical or related psychosocial records. Based on all available information, two independent senior psychiatrists, who were blind to group status, provided final diagnoses by DSM-IV, DSM-III, and Research Diagnostic Criteria. Disagreements were resolved by consensus.

Probands were classified as bipolar spectrum (n=38) if they received lifetime DSM diagnoses of bipolar I or bipolar II disorder (68% had bipolar I disorder). The bipolar I and bipolar II participants did not differ in startle magnitude during or following affective stimuli (Fs<1, Ps>0.85), and therefore all were included in a single bipolar group for analyses. Number of lifetime episodes of major depression was determined during diagnostic interviews. Based on interview data, clinicians quantified participants' total lifetime episodes as 0, 1, 2, 3 or more, or "too numerous to count". The participants in the last category had experienced so many depressive episodes that clinicians conducting the interviews judged that it would not be valid or feasible to enumerate the total. This particularly seemed to be the case for some participants with bipolar disorder who had experienced frequent and fairly rapid pole switching. At the time of the physiological assessment, symptomatic status was assessed using the Beck Depression Inventory (BDI; Beck et al., 1988a) and the Beck Anxiety Inventory (BAI; Beck et al., 1988b), valid and reliable self-report symptom scales.

2.3. Experimental paradigm

Participants viewed 36 digitized pictures from the International Affective Picture System (IAPS; Lang et al., 1999). Twelve pleasant (e.g., an ice cream cone), 12 neutral (e.g., a rolling pin), and 12 unpleasant pictures (e.g., a mutilated face)[1] were presented on a 21-in computer screen located 5 ft from the participant. Pictures were selected based on normative IAPS ratings (Lang et al., 1999). High- or low-valence pictures were used for pleasant and unpleasant conditions, respectively, and high-arousal pictures were used for both conditions. Moderate-valence, low-arousal pictures were used for the neutral condition. As expected, participants rated pictures in the pleasant category as more pleasant than those in the unpleasant category [t(134)=21.63, P<0.001], rated pleasant and unpleasant pictures as equally high in arousal [t(134)=−1.89, P>0.05], and rated pictures in both conditions as higher in arousal than those in the neutral condition [t(134)=12.48 and t(134)=−13.07, respectively, Ps<0.001]. Because of gender differences in normative responses, men and women viewed slightly different sets of pictures. The content of the pictures was deemed appropriate for the current sample because the IAPS pictures have been used in previous studies with clinical samples of adults (e.g., Allen et al., 1999). The startle probe was a 50-ms burst of 100-dB white noise with instantaneous rise time that was presented binaurally through EAR-3A earphones (Aearo Company). A James Long Company STIM stimulus presentation system delivered the visual and auditory stimuli (JLC, Caroga Lake, NY, USA).

Following standard procedures, the startle paradigm involved passive viewing of affective stimuli. Participants were told that noises might occur and were instructed to attend to the images on the monitor. Pictures were presented in three counterbalanced blocks, with each block containing four pictures from each affective category. Unipolar, bipolar, and control groups did not differ in the order in which they viewed stimulus blocks. Each picture was presented on a computer monitor for 6 s, and the acoustic startle probe was presented 3, 4, or 5 s after picture onset. Within each block, one picture in each affective condition was presented without a startle probe. Intertrial intervals (ITIs) were 9.5, 11.5, and 13.5 s and were varied randomly so that participants would not habituate to stimulus timing. Two probes were presented before the first picture. Four probes were presented during ITIs, two after pleasant pictures, and two after unpleasant pictures. The intervals between picture offset and ITI probe presentation were 4.5 and 5.5 s for the pleasant pictures and 5.5 and 6.5 s for the unpleasant pictures. Because the physiologic and

[1] The following IAPS pictures were used: 1120, 1300, 2190, 3000, 3010, 3030, 3120, 3130, 3150, 3170, 3530, 4650, 4660, 4680, 5510, 5530, 6230, 7000, 7010, 7050, 7060, 7080, 7090, 7100, 7150, 7230, 7270, 7330, 7700, 8080, 8200, 9250 (all participants); 4180, 4210, 4250, 4310 (men only); 4470, 4490, 4510, 4520 (women only).

expressive changes associated with an emotion are postulated to last on the order of seconds (Ekman, 1984; Oatley and Jenkins, 1996), we considered the interval between picture offset and ITI probe to be adequate to measure recovery from emotion.

Following the startle paradigm, participants viewed the pictures a second time and rated the valence (from unpleasant to pleasant) and arousal (from calm to aroused) of their own response using the 9-point visual Likert-type scales of the Self-Assessment Manikin (SAM; Bradley and Lang, 1994). Due to time constraints, one male control participant did not complete ratings. During the task, an experimenter monitored participants' level of drowsiness and attention. Excessive drowsiness led three additional participants to be excluded from analyses. An observer coded participants' videotaped behavior for looking away during the task (present or absent).

2.4. Physiological recording and quantification

Startle blink response was recorded using two 6-mm tin electrodes placed 1 cm apart underneath the right eye (Fridlund and Cacioppo, 1986). Electrode impedances were less than 20 kΩ and were checked before and after the session. The electromyographic (EMG) signal was collected and quantified with equipment and software from the James Long Company. The bioamplifier was set for bandpass filtering with half-power cutoff frequencies of 1 and 1000 Hz (12-dB/octave rolloff). The gain was 5000. Data were digitized continuously at 512 Hz. Because the maximum frequency of the range defined for the blink signal was 240 Hz, which is less than one half of the sampling rate, it is unlikely that this sampling rate resulted in aliasing. Physiological data were time-locked to the presentation of visual and auditory stimuli. After acquisition, EMG data channels were stripped from other physiology channels and saved to a separate file.

EMG data were processed offline using methods described previously (Jankel et al., 1999; Schmidt et al., 1998). Trials were rejected if blink-related EMG activity occurred in the 200-ms period before to the startle probe. As a result, 3% of trials were rejected. Fourier analyses were used to quantify the power in each successive 32-ms epoch for a band from 80 to 240 Hz. We focused on this spectral band to maximize the EMG signal-to-noise ratio and the short-latency timing precision of startle blinks. The software identified the peak EMG power in a 180-ms window after the onset of the startle probe. No participant failed to respond to more than four trials, and no participants were excluded for lack of responsiveness. Following the correction applied to skewed blink data in other studies (e.g., Patrick et al., 1993), EMG power for each trial was transformed to a within-participant T score (M=50, SD=10). This served to standardize startle magnitude for comparisons across participants. Mean T scores were then computed for each participant's responses to the pleasant, neutral, and unpleasant picture conditions, as well as to post-pleasant and post-unpleasant ITI conditions.

2.5. Data analyses

Repeated measures analyses of variance (ANOVAs) were conducted, with sex and group as between-subjects factors, affective condition (i.e., pleasant, neutral, or unpleasant) as a within-subjects factor, and age as a covariate. Following findings of a Group-by-Condition interaction effect, *within-group* pairwise contrasts of conditions were conducted. This approach was taken because affect-modulated startle is evident as a linear change across affective conditions. Typical modulation is evident as an increase in blink magnitude from pleasant to unpleasant conditions (e.g., Patrick et al., 1993), but because group differences may also be evident in differences between neutral and pleasant (see Allen et al., 1999) or neutral and unpleasant conditions, all pairs of conditions were examined for change in startle. Consistent with this approach, between-group differences in single affective conditions were not considered.

3. Results

Based on BDI (Beck et al., 1988a) and BAI (Beck et al., 1988b) self-reports, COD participants had higher levels of depression (M=10.84, SD=9.44) and anxiety (M=10.39, SD=8.18) symptoms than did controls [M=1.88, SD=2.38; $F(1,134)$=51.35, P<0.001;

M=2.73, SD=2.82; $F(1,134)$=48.02, P<0.001, respectively]. Unipolar, bipolar, and control groups also differed in current depression [$F(2,133)$=25.66, P<0.001] and anxiety symptoms [$F(2,133)$=25.16, P<0.001]. Post hoc Tukey comparisons indicated that the unipolar and bipolar groups had higher levels of depression (M=10.42, SD=9.59 and M=11.26, SD=9.39, respectively) and anxiety symptoms (M=11.42, SD=7.95 and M=9.36, SD=8.39, respectively) than did controls (Ps<0.001), but the two groups did not differ from each other. Pearson correlations indicated that age of onset of depression was unrelated to self-reported emotional responses to pictures (r=−0.20–0.09, Ps>0.05) and to raw blink magnitude (r=−0.12–−0.004, Ps>0.30).

Table 1 presents groups' affective ratings and raw blink magnitude. The unipolar, bipolar, and control groups did not differ in the self-reported valence or arousal of their response to affective stimuli. There was a Sex-by-Condition interaction effect for valence [$F(2,129)$=4.35, P<0.05] and arousal [$F(2,129)$=7.37, P<0.001]. Follow-up analyses indicated that women rated pleasant and unpleasant pictures as less pleasant (pleasant: M=6.32, SD=1.02 for men, M=5.69, SD=1.09 for women; $F(1,133)$=10.71, P<0.005; unpleasant: M=3.14, SD=1.12 for men, M=2.51, SD=1.08 for women; $F(1,133)$=10.16, P<0.005] and rated unpleasant pictures as more arousing than did men [M=3.37, SD=1.70 for men, M=4.21, SD=1.98 for women; $F(1,133)$=5.90, P<0.05]. Unipolar, bipolar, and control groups did not differ in their raw blink magnitude to startle probes presented in the absence of affective stimuli [F=0.48, P>0.60].

Table 1
Mean (SD) of affective stimulus ratings and raw blink magnitude

Ratings	Group		
	Control	Unipolar	Bipolar
Valence			
Pleasant	5.85 (1.01)	6.01 (1.18)	5.81 (1.25)
Neutral	4.95 (0.44)	4.86 (0.56)	4.48 (1.23)
Unpleasant	2.60 (1.15)	2.80 (1.09)	2.75 (1.19)
Arousal			
Pleasant	3.69 (1.81)	3.48 (1.96)	3.51 (1.67)
Neutral	1.76 (1.33)	1.86 (1.25)	1.60 (1.01)
Unpleasant	3.97 (1.89)	3.98 (2.05)	3.78 (1.87)
Blink magnitude (μV)			
Pleasant	27.04 (25.71)	30.62 (30.11)	26.60 (28.90)
Neutral	28.60 (26.23)	35.12 (33.81)	25.12 (30.86)
Unpleasant	35.76 (30.58)	38.28 (38.24)	27.60 (33.83)
ITI	26.85 (30.20)	26.02 (27.00)	19.15 (26.55)

Note: ITI=intertrial interval. Ratings were on a 9-point scale.

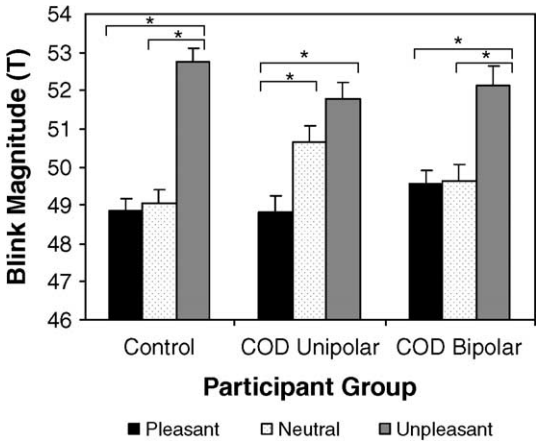

Fig. 1. Mean startle response of control, COD unipolar, and COD bipolar groups during pleasant, neutral, and unpleasant affective stimuli. Error bars represent one standard error (SE) of the mean. An asterisk (*) indicates that two conditions differed within group at P<0.05.

3.1. The influence of unipolar or bipolar course

3.1.1. Startle during affective stimuli

To test the hypothesis that unipolar, bipolar, and control groups would differ in startle across affective conditions, a repeated-measures ANOVA was conducted. There was a Group-by-Condition interaction effect [$F(4,266)$=2.48, P<0.05; see Fig. 1]. Within-groups pairwise contrasts for conditions indicated that although both the unipolar and bipolar groups exhibited a linear blink response across all three affective conditions [$F(1,37)$=13.32, P<0.005 and $F(1,37)$=12.33, P<0.005, respectively], they differed in their pattern of response between pairs of conditions. Whereas the bipolar group, like the control group, exhibited a larger response during the unpleasant relative to the neutral condition [$F(1,37)$=10.03, P<0.005 and $F(1,59)$=50.25, P<0.001, respectively], the unipolar group exhibited a similar response between these conditions (F=2.77, P>0.10). In addition, the unipolar group exhibited a larger response during the neutral relative to the pleasant condition

[$F(1,37)=6.41$, $P<0.05$], but the bipolar and control groups did not (Fs<0.20, Ps>0.65). The main effect for Condition was not significant ($F=1.37$, $P=0.26$).[2]

In addition, a repeated-measures ANOVA was conducted to test whether the unipolar, bipolar, and control groups differed in startle during pictures vs. startle during ITI. The Group-by-Condition interaction was not significant [$F(2,135)=0.23$, $P>0.70$], indicating that any change in startle response between affective and non-affective contexts was consistent across groups.

3.1.2. Startle following affective stimuli

To test the hypothesis that the unipolar group would display enhanced startle following unpleasant stimuli, a repeated-measures ANOVA was conducted on standard scores for blink magnitude during post-picture ITIs. Affective condition (post-pleasant or post-unpleasant) was a within-subjects variable, and bipolar course group was a between-subjects variable. There was a Group-by-Condition interaction [$F(2,135)=4.16$, $P<0.05$; see Fig. 2]. Separate within-group repeated measures ANOVAs indicated a significant Condition effect in the control group [$F(1,59)=17.19$, $P<0.001$] and a statistical trend for Condition in the unipolar group [$F(1,37)=3.71$, $P=0.06$], with both groups exhibiting larger startle magnitude after unpleasant than after pleasant stimuli. The bipolar group exhibited no difference between conditions, however ($F=0.001$, $P>0.95$).

To examine whether the lack of difference between post-pleasant and post-unpleasant conditions in the bipolar group reflected affect regulation rather than lack of affective reactivity, three sets of follow-up analyses were conducted. First, within-group repeated measures ANOVAs were conducted to test whether all three groups exhibited differences in startle magnitude during vs. following affective stimuli. Pleasant and unpleasant conditions were examined separately. Within each group, the Condition effect was non-

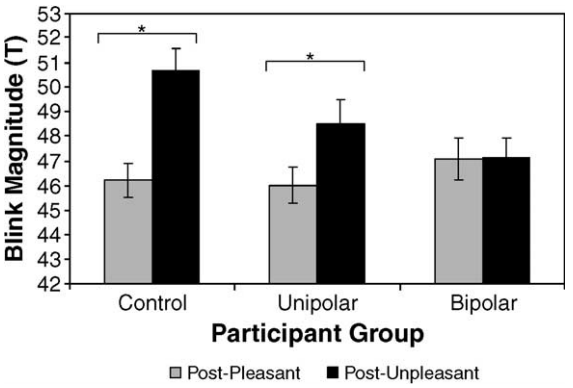

Fig. 2. Mean startle magnitude after pleasant and unpleasant affective stimuli in control, COD unipolar, and COD bipolar groups. Error bars represent one *SE* of the mean. An asterisk (*) indicates that two conditions differed within group at $P<0.05$.

significant: all three groups exhibited a smaller blink following affective stimuli than during affective stimuli [$F(1,59)=13.72$, $P<0.001$; $F(1,37)=12.54$, $P<0.005$; and $F(1,37)=7.14$, $P<0.05$ for the pleasant condition; $F(1,59)=4.60$, $P<0.05$; $F(1,37)=7.79$, $P<0.01$; and $F(1,37)=20.97$, $P<0.001$ for the unpleasant condition; for control, unipolar, and bipolar groups, respectively]. This indicates that the bipolar group did not simply exhibit low reactivity, which would have been evidenced by low blink magnitude both during and after unpleasant stimuli. Second, a regression analysis was conducted for each group, in which startle during affective stimuli was the predictor and startle after stimuli was the dependent variable. Pleasant and unpleasant conditions were examined separately. The regression model for the unpleasant condition was significant for the bipolar group ($F=4.54$, $P<0.05$), but the models for the control and unipolar groups were not (Fs=1.66 and 1.78, Ps>0.15). The regression models for the pleasant condition were nonsignificant for all three groups (Fs=0.10–2.09, Ps>0.15). This indicates that the magnitude of startle during unpleasant stimuli was associated with that after stimuli only for the bipolar group. Finally, exploratory ANOVAs were conducted with raw blink scores to examine whether the bipolar group exhibited a lower blink magnitude than the other groups during either affective condition. Results indicated that the three groups did not differ in startle magnitude during either

[2] Group differences in raw blink magnitude across conditions were also analyzed, and results did not differ greatly from the pattern found with standard scores for blink magnitude. The Group-by-Condition effect became a statistical trend ($F=3.05$, $P=0.05$), and the pattern of pairwise comparisons was similar.

pleasant or unpleasant stimuli (Fs<1.07, Ps>0.30). Together, these results indicate further that the bipolar did not simply fail to respond to unpleasant stimuli.

3.2. Influence of number of lifetime depressive episodes

To test the hypothesis that participants with a high number of depressive episodes would differ in startle modulation during affective conditions, the COD group as a whole was divided into the following subgroups: *1–2 episodes* (n=31; 12 bipolar), *3 or more episodes* (n=31; 15 bipolar), or *episodes too numerous to count* (n=9; 7 bipolar). The unipolar and bipolar groups did not differ in the number of lifetime depressive episodes they had experienced [$\chi^2(N=76, df=3)=6.19$, $P>0.10$], and therefore bipolar status was not included in analyses.

There was a Group-by-Condition interaction [$F(6,138)=2.14$, $P<0.05$] for blink magnitude during affective conditions (Fig. 3). Within-group pairwise contrasts indicated that the "too numerous" group did not exhibit a change in blink magnitude across affective conditions [$F(1,8)=1.59$, $P>0.20$]. Both the group with 1–2 episodes and the group with 3 or more episodes, however, exhibited the typical increase in startle magnitude from pleasant to unpleasant conditions [$F(1,29)=11.93$, $P<0.005$ and $F(1,30)=21.73$, $P<0.001$, respectively].

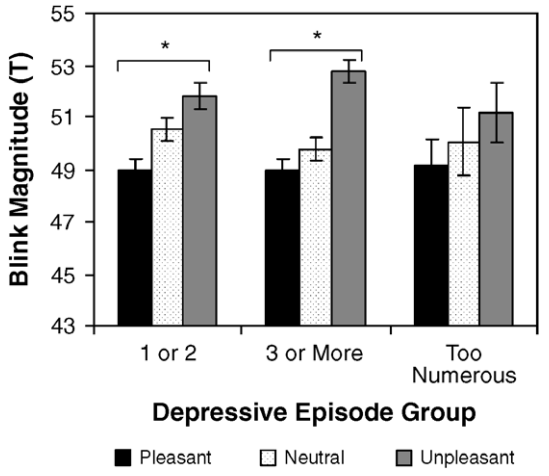

Fig. 3. Mean startle magnitude of COD participants during pleasant, neutral, and unpleasant affective conditions, by number of lifetime major depressive episodes. Error bars represent one *SE* of the mean. An asterisk (*) indicates that two conditions differed within group at $P<0.05$.

3.3. Influence of psychiatric comorbidity

Because affect-modulated startle is abnormal in anxiety disorders (Grillon et al., 1997, 1998; Lang, 1995) and psychopathy (Patrick et al., 1993), we examined whether a history of anxiety disorder or antisocial personality disorder in the COD group influenced startle responding. COD participants with and without a history of these comorbid diagnoses did not differ in their startle response in the absence of affective stimuli (Fs<1, Ps>0.50), and repeated-measures ANOVAs indicated a nonsignificant Group-by-Condition interaction for blink magnitude during or following affective stimuli (Fs=0.02–3.19, Ps>0.10).

3.4. Influence of current depression symptoms

Because Allen et al. (1999) reported that a high-severity subgroup of depressed adults displayed abnormal startle modulation, we conducted repeated-measures ANCOVAs for startle during and following affective stimuli, with depressive or anxiety symptoms as a covariate. The Symptoms-by-Condition interaction was not significant in either analysis (Fs=1.40 and 1.80, Ps>0.10).

3.5. Attention and subjective response as possible confounds

Post hoc analyses examined the possibility that startle-modulation differences between unipolar, bipolar, and control groups were due to differences in attention or subjective response. Chi-square tests indicated that the unipolar, bipolar, and control groups were equally likely to attend to affective stimuli ($\chi^2=2.11$, $P>0.15$). The role of subjective response was tested by repeating the original analyses with bipolar group but including only participants with typical ratings for affective valence (>1 *SD* above the mean for pleasant; within 1.5 *SD* of the mean for neutral; and >1 *SD* below the mean for unpleasant stimuli). Results did not differ from the original results.

4. Discussion

The current study examined the affective modulation of the startle blink response in a well-characterized sample of adults with COD and either unipolar or bipolar course. In comparison with adults who had no history of major psychopathology, unipolar adults evidenced differences in the startle response during exposure to affective stimuli, and bipolar adults evidenced differences following such exposure. Unipolar adults differed from controls and bipolars by displaying startle attenuation to pleasant stimuli but not displaying startle potentiation to unpleasant stimuli. Bipolar adults appeared to display a more rapid recovery after unpleasant stimuli than did controls. Participants with the most numerous depressive episodes failed to display modulation of the startle response across affective categories.

Contrary to our predictions, unipolar course was associated with greater sensitivity to pleasant stimuli and with low sensitivity to unpleasant stimuli. This pattern of response differs from previous theoretical and experimental accounts of depression. For instance, other studies have reported that adults with depression or dysphoria display inappropriate responses to pleasant stimuli, from failing to exhibit expected facial muscle activity (Sloan et al., 2002) to showing reduced facial expressiveness or increased startle response (Allen et al., 1999; Sloan et al., 2001). The apparently enhanced responding to pleasant stimuli in the current study is also surprising in light of the finding that such responding occurs in adults with high positive affect (Hawk and Kowmas, 2003).

The pattern of startle responding in unipolar depression may reflect the familiar and unsurprising nature of unpleasant stimuli to adults with a long history of unipolar depression. This history of psychiatric disorder distinguishes participants in the current study from those in other studies, which have often focused on normal individual differences or subclinical depression. Responses to both pleasant and unpleasant stimuli may be disrupted in adults who have experienced depression early in life. Adults with depression show sustained amygdala activation in response to unpleasant stimuli (Siegle et al., 2002), and accordingly, unipolar COD adults may be accustomed to experiencing negative affect and may fail to respond to unpleasant stimuli as if they are distressing. Unipolar adults may experience positive affect infrequently and in low intensity, however, and they consequently may find pleasant stimuli more affecting in comparison to neutral stimuli.

The bipolar group differed from the unipolar and control groups in the pattern of startle response after, but not during, exposure to affective stimuli. Specifically, the bipolar group exhibited similar startle magnitude after pleasant and unpleasant stimuli. We had not expected the bipolar group to differ from the other groups after picture viewing, and this finding may indicate that the bipolar group differed from the unipolar and control groups in recovering from negative affect. In considering this finding, it is useful to consider the affective processes of modulation and maintenance, where modulation involves changing the intensity or quality of an affective response and maintenance involves influencing the duration of an affective response. While the unipolar group exhibited atypical modulation during stimuli, the bipolar group exhibited atypical maintenance after stimuli. Decreased maintenance of affective response in bipolar disorder may reflect the affective lability characteristic of the disorder, as well as a tendency to shift attention quickly during affective contexts (Murphy et al., 1999). Thus, although COD may involve poor affective regulation generally, modulation and maintenance of affect may be differentially disrupted in unipolar and bipolar forms.

That participants with a high number of depressive episodes appeared to have a blunted startle response across affective categories suggests that recurrence has important consequences for affect regulation. This blunted response means that although these participants exhibited the predicted failure to inhibit startle during pleasant contexts, they failed to respond to unpleasant contexts with the predicted potentiation. The lack of potentiation to unpleasant stimuli is consistent with the previous study on startle in major depressive disorder (Allen et al., 1999). In line with our findings, interpretations of affective response in adult depression have emphasized affective stereotypy and lack of selective responsiveness (e.g., Rottenberg et al., 2002). In comparison with controls, depressed adults have failed to report a similar increase in sadness in response to a sad film (Rottenberg et al., 2002), failed to show similar sensitivity of event-

related brain potentials to affective valence (Deldin et al., 2001), and exhibited reduced neural activation to facial expressions (Lawrence et al., 2004). The evidence thus points to the possibility that recurrent depression involves the dampening of physiological processes related to affect regulation, rather than the enhancement of response to unpleasant stimuli.

A possible interpretation of our findings on bipolar course and recurrence in affect-modulated startle is that, perhaps due to current levels of depression, the unipolar group or the high-episode group did not attend to the affective stimuli or did not find the unpleasant stimuli to be distressing. Neither of these explanations appears to be viable, however. The probability of looking away from affective stimuli was similar across bipolar course groups and depressive episode groups, implying that differences in attention were not responsible for physiological differences. The subjective experience of the intensity and quality of the stimuli was similar across all groups, regardless of unipolar course or chronicity.

The discontinuity between self-reported experience and a physiological index of affect regulation is consistent with at least one prior study. During happy and sad imagery, depressed adults exhibited lower facial muscle activity than did control adults, despite similar self-reported affect (Gehricke and Shapiro, 2000). Together with the current findings, this suggests that unipolar depression may involve a dissociation between subjective and physiological components of affective response and may compromise physiological processes related to affect regulation.

Another issue relevant to interpreting the unipolar group's pattern of response concerns its reactions to neutral stimuli. Although Fig. 1 appears to indicate that the unipolar group had a greater startle response to the neutral condition, the unipolar, bipolar, and control groups did not differ in raw blink magnitude during this condition. Startle during neutral conditions is sensitive to affective meaning (Lawson et al., 2002), however. It is still possible that the unipolars' lack of difference in blink magnitude between unpleasant and neutral conditions reflects a cognitive bias in which both conditions are experienced as aversive. Perhaps as a result of responding to benign stimuli as though they were aversive, the unipolar group may have exhibited the same startle magnitude to neutral stimuli as other groups in absolute terms, while simultaneously exhibiting a large startle to neutral relative to their own responses overall.

The current study is the first to test the contributions of both past and current depression to affect-modulated startle. Current depressive symptoms did not influence the startle modulation of the unipolar or bipolar groups. Startle may be more sensitive to trait than to state features of depression (Grillon and Baas, 2003), and previous studies have indeed found little consistent relation between current depressive symptoms and affect-modulated startle (Cook, 1999; Hawk et al., 2001). Published reports that *have* found depression-related abnormalities are few and inconsistent. In one study, the depressed group exhibited an increase in startle magnitude during unpleasant states (Cook et al., 1991), but in another, a severely depressed subgroup exhibited potentiation during the pleasant affective condition (Allen et al., 1999). Such lack of convergence in the literature could reflect sample differences: one study assessed undergraduate students without diagnoses (Cook et al., 1991) and the other examined adult inpatients who ranged in age from 23 to 57 years (Allen et al., 1999).

Our findings are informed by the following findings on resting physiology, task-related physiology, and behavior from the larger multidisciplinary project. Women with COD exhibit right frontal electroencephalographic asymmetry at rest, a characteristic associated with depression and withdrawal from unpleasant stimuli (Miller et al., 2002). This finding was especially pronounced in women with a bipolar course. Unlike that study, we did not find that gender, comorbid diagnoses, or severity of current symptoms were important sources of variability. COD adults with unipolar or bipolar course exhibit low resting vagal tone, which is related to poor affect regulation (Santucci et al., 2004). Offspring of adults with COD use less effective behavioral strategies for affect regulation during an affective challenge (Silk et al., in press) and show poor heart period recovery after a disappointing experience (Forbes et al., under review). Together, these findings support the claim that COD (or a parent history of COD) involves difficulty with affect regulation.

The results of the current study should be interpreted in light of its limitations, which include the assessment of startle modulation at a single time

point and the focus on diagnostic history rather than current episode. Further, our inclusion of adults with COD and not those with adult-onset depression precludes a definite statement as to whether the differences we found are indeed developmental in origin or could characterize depression in general.

In summary, our study of adults with a history of COD indicates that psychophysiological indices of brain function related to affect regulation may enrich the clinical characterization of such early-onset phenotypes. One intriguing question is whether the presumptive impairments are pre-depression trait markers or negative developmental sequelae of childhood-onset depression. Thus, it would be valuable to examine youngsters at risk for mood disorders, as well as to conduct longitudinal investigations of affect regulation in children and adolescents with COD. Our findings also highlight the importance of considering age of onset, lifetime diagnostic course, and recurrence when conducting research on the psychophysiology of mood disorders.

Acknowledgments

This study was supported by NIMH Program Project MH56193, a NSF Graduate Research Fellowship, NIMH Fellowship MH18951, MHIRC Seed Award MH30915, and a NARSAD-Educational Foundation of America Award.

We thank the staff of Program Project MH56193, particularly Valerie Monaco and Chelsea Jankel for technical contributions and Charles George and Marc Ware for statistical consultation. We are also grateful to Drs. Cynthia Last, Debbie Beidel, Sam Turner, Rolf Loeber, Neil Ryan, David Brent, Michael Sayette, and Mary Fristad for their help in accessing former participants from studies of childhood psychiatric disorders.

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