Psychophysiology, 47 (2010), 659–668. Wiley Periodicals, Inc. Printed in the USA.

DOI: 10.1111/j.1469-8986.2010.00977.x

Low baseline startle and deficient affective startle modulation in remitted bipolar disorder patients and their unaffected siblings

STELLA G. GIAKOUMAKI,[a,b] PANOS BITSIOS,[a,b] SOFIA FRANGOU,[b] PANOS ROUSSOS,[a] INGRID AASEN,[c] ADRIAN GALEA,[d] AND VEENA KUMARI[c]

[a]Department of Psychiatry & Behavioral Sciences, Faculty of Medicine, University of Crete, Heraklion, Greece
[b]Section of Neurobiology of Psychosis, NIHR Biomedical Research Centre for Mental Health and Institute of Psychiatry, King's College London, London, UK
[c]Department of Psychology, Institute of Psychiatry, King's College, London, London, UK
[d]Division of Psychological Medicine, Institute of Psychiatry, King's College, London, London, UK

Abstract

We examined whether startle abnormalities are present in bipolar disorder (BD) patients and their unaffected siblings. Twenty-one remitted patients with BD, 19 unaffected siblings, and 42 controls were presented with 18 pleasant, 18 unpleasant, and 18 neutral pictures. Acoustic probes (104 dB) were presented during 12 of 18 pictures in each affective category at 300, 3000, and 4500 ms after picture onset, so that there were 4 pictures per valence per probe onset type. Baseline startle was assessed during blank screens and was found reduced in patients and sibling groups. We found startle inhibition with the 300 probes and a linear increase in amplitude with valence with the late probes in controls; these effects were absent in patients and their siblings. Low startle and blunted startle reactivity may represent trait deficits in remitted BD patients and their relatives, possibly associated with attentional deficits and adaptive down-regulation of emotion.

Descriptors: Bipolar disorder, High risk, Trait deficit, Startle, Affective pictures, Affect dysregulation

Mood disorders are defined by abnormalities in regulation of affect and in emotional information processing (Goodwin & Jamison, 2007; Panksepp, 1998). A key challenge for the field of affective neuroscience is to clarify how mood disorders alter affective reactivity. The paradigm of affective startle modulation lends itself to the study of altered affective reactivity in mood disorders (for reviews, see Grillon, 2002; Lang & Davis, 2006). Affective modulation of the startle reflex has been conceptualized as reflecting a "priming" effect on neural circuits toward an appetitive or aversive orientation based on an individual's baseline state (Lang, 1995; Lang, Bradley, & Cuthbert, 1990, 1997). According to this model, neural networks are primed to react to stimuli that are consistent with the individual's currently engaged motivational system. Because the eyeblink startle is a defensive reflex, it is potentiated or attenuated depending on whether an individual is in a negative or positive affective state, respectively. A large body of evidence has established that in healthy individuals the magnitude of the startle reflex increases with increased negative valence of the foreground stimuli and is attenuated during exposure to positive stimuli (Bradley, Cuthbert, & Lang, 1990; Cook, Davis, Hawk, Spence, & Gautier, 1992; Hamm & Vaitl, 1996; Vrana, Spence, & Lang, 1988). Consequently, affective modulation of the startle response can be a useful tool when one examines affective reactivity (Grillon & Baas, 2003).

Currently, there are three models on the relationship between mood disorders and affective reactivity that may receive experimental support from startle studies. The positive attenuation hypothesis is based on clinical deficits in motivational behavior (American Psychiatric Association, 2000) and experimental evidence of reduction in reactivity when individuals experiencing depressive symptoms respond to pleasant stimuli (e.g., pleasant pictures or amusing film clips; Rottenberg, Kasch, Gross, & Gotlib, 2002; Sloan, Strauss, & Wisner, 2001). This attenuation in reactivity in depressed patients has also been noted in response to positive stimuli during the affective startle (Allen, Trinder, & Brennan, 1999; Rottenberg, Gross, & Gotlib, 2005). However, there is evidence of an effect of diagnosis from a single study by Forbes, Miller, Cohn, Fox, and Kovacs (2005). They reported

S.G.G. was supported by an honorary postdoctorate fellowship by the Greek State Scholarship Foundation and a "Propondis Foundation" scholarship. P.R. was supported by a Manasaki Foundation scholarship. V.K. is supported by the Wellcome Trust, UK (067427/z/02). These funding/support bodies had no role in the design and conduct of the study, in collection, management, analysis and interpretation of the data, and in preparation, review, or approval of the manuscript. The authors of this paper do not have any financial interests or conflicts to disclose in connection with this manuscript.

Address reprint requests to: Panos Bitsios, Department of Psychiatry & Behavioral Sciences, Faculty of Medicine PO BOX 2208, University of Crete, Heraklion 71003, Crete, Greece. E-mail: pbitsios@med.uoc.gr

PSYCHOPHYSIOLOGY

that, despite comparable depressive symptomatology, patients with Bipolar Disorder (BD) had preserved reactivity to pleasant images whereas those with Major Depressive Disorder (MDD) showed the expected attenuation.

The negative potentiation model was also inspired by clinical observations that depressed individuals exhibit negative affect and cognitions (Beck & Koenig, 1965). This is supported by findings of increased startle potentiation during the viewing of aversive pictures in healthy individuals scoring high on negative affect (Cook, Hawk, Davis, & Stevenson, 1991). However, studies in individuals with clinical depression (Allen et al., 1999; Dichter & Tomarken, 2008; Forbes et al., 2005; Kaviani et al., 2004) have been consistent in reporting blunted, rather than enhanced, startle reactivity to unpleasant stimuli, irrespective of the primary diagnosis (be it MDD or BD).

The emotion-context insensitivity model (Rottenberg & Gotlib, 2004) was primarily proposed in an attempt to synthesize the findings of diminished emotional reactivity to both negative and positive stimuli in depressed individuals. This model views depression as a state of disengagement from the environment that prevents any action. This model receives support from startle studies in more severely depressed and anhedonic individuals reporting blunted startle reactivity to both pleasant and unpleasant stimuli and an underreactive baseline startle (Allen et al., 1999; Kaviani et al., 2004; O'Brien-Simpson, Di Parsia, Simmons, & Allen, 2009).

There are two major issues with the proposals outlined above that are relevant to this study. First, they may be useful heuristic models of depressive states but they probably fail to capture disease-related changes in reactivity. Specifically, the pattern of diminished reactivity to both positive and negative stimuli observed in depressed MDD patients is not present in those who are recovering (Allen et al., 1999; Dichter, Tomarken, Shelton, & Sutton, 2004) or have recovered and are asymptomatic (Rottenberg et al., 2005). As already mentioned, positive attenuation may differentiate MDD from BD depressive states.

The second issue relates to changes in emotional reactivity in connection to genetic predisposition to mood disorders. Epidemiological studies have established that first-degree relatives of patients with mood disorders (both MDD and BD) are at high risk for affective morbidity that is expressed as increased rates of clinically diagnosable conditions (Shih, Belmonte, & Zandi, 2004) or personality traits (Kesebir et al., 2005; Mendlowicz, Jean-Louis, Kelsoe, & Akiskal, 2005; Vázquez et al., 2008). Existing data although limited to severe MDD show blunted baseline startle reactivity (Allen et al., 1999; Kaviani et al., 2004; O'Brien-Simpson et al., 2009), which has been linked to risk for depressive relapse in recovered depressives (O'Brien-Simpson et al., 2009). Interestingly, early (attentional) startle modulation as measured by the prepulse inhibition paradigm and baseline startle are 50% and 70% heritable, respectively (Anokhin, Golosheykin, & Heath, 2007; Anokhin, Heath, Myers, Ralano, & Wood, 2003; Carlson, Katsanis, Iacono, & McGue, 1997) whereas the evidence for heritability of the affective startle modulation in humans is inconsistent (Anokhin et al., 2007; Carlson et al., 1997).

In the present study, consistent with common methodology to assess for traitlike, vulnerability phenotypes, we included remitted patients to avoid the confounding state-dependent influence of florid symptoms and their unaffected relatives in order to remove possible confounds of both symptoms and medication. We presented the startle probes at early and late intervals after picture onset. Startle elicited by probes delivered early and late in the viewing window makes it possible to investigate attentional and emotional mechanisms involved in the early and later stages, respectively, of affective picture processing (Bradley, Cuthbert, & Lang, 1993, 1999; Lang et al., 1997). Startle is normally attenuated in the early stages of all categories of affective picture viewing, and this early startle attenuation is an example of prepulse inhibition (PPI), whereby picture presentation serves as a prepulse (Bradley et al., 1993).

Within the context of the explanatory models of altered affective reactivity in mood disorders and relevant findings from startle literature highlighted above, the study had two aims. The first aim was to examine early (PPI) and late (affective) modulation of the startle reflex and the unmodulated baseline startle in remitted Bipolar-I (BD-I) patients. On the basis of evidence for PPI deficits in remitted BD-I patients (Giakoumaki et al., 2007), we expected to find deficient early startle modulation in our patient sample. The study of Forbes et al. (2005) refers to symptomatic BD-I and BD-II patients and, as such, could not safely guide predictions with regards to baseline startle and its affective modulation in our study where hypotheses are tempered by remission status. Given that most of our patients were likely to have a history of moderate to severe depressive episodes and given the findings of O'Brien-Simpson et al. (2009) in remitted MDD patients, we hypothesized that our patient group would present with attenuated startle reactivity. There are no reports on affective startle reactivity in remitted BD-I patients to date. Therefore, our hypotheses were guided by the literature on (a) temperament and personality traits (Cloninger, Svrakic, & Przybeck, 1993) most relevant to remitted BD and (b) the Behavioral Activation (or Approach) System (BAS) (Gray, 1982, 1991, 1994), the overactivity and underactivity of which is postulated to underlie the high and low moods respectively that characterize bipolar spectrum disorders (Depue & Iacono, 1989; Depue, Krauss, & Spoont, 1987; Fowles, 1988, 1993; Gray, 1991).

We considered BAS underactivity to be more pertinent to remitted BD status, because BAS overactivity is consistent with a currently manic state (Urosević, Abramson, Harmon-Jones, & Alloy, 2008). It is relevant in the respect that subjects scoring low in BAS show reduced affective startle modulation (Hawk & Kowmas, 2003). With regard to personality and temperament traits, Cloninger's novelty seeking has been repeatedly found elevated in BD (Haro et al., 2007; Nery et al., 2008; Olvera et al., 2009; Tillman et al., 2003; Young et al., 1995) with some evidence for specificity to remitted BD status as opposed to harm avoidance or other temperament traits (Young et al., 1995). Subjects with high novelty seeking present with reduced affective startle modulation (Roussos, Giakoumaki, & Bitsios, 2009). Novelty seeking is also considered a measure of reduced fear, and low fear subjects do not show the expected startle potentiation to aversive pictures (Benning, Patrick, & Iacono, 2005; Cook et al., 1992; Patrick, Bradley, & Lang, 1993; Vaidyanathan, Patrick, & Bernat, 2009). On the basis of the above findings on these subclinical but relevant-to-BD temperament and personality traits, we predicted reduced affective startle modulation in the patient group.

The second aim of the study was to investigate, for the first time, early (PPI) and late (affective) modulation of the startle reflex and the baseline startle in unaffected first-degree relatives of BD patients. Given the similarities in affective morbidity between BD-I patients and their first degree relatives and the genetic mediation of the personality traits mentioned above (Bouchard & McGue, 2003), we predicted that relatives in our

sample would probably show affective startle modulation abnormalities similar to those of their affected probands. Moreover, given the high heritability of baseline startle and PPI (Anokhin et al., 2007) and evidence for PPI deficits in remitted Bipolar-I patients and their unaffected siblings (Giakoumaki et al., 2007), we expected to find attenuated baseline startle reactivity and deficient early startle modulation in the siblings group.

Materials and Methods

Participants

The study was approved by the local research ethics committees. All patients were outpatients with Bipolar-I as defined in the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*; American Psychiatric Association, 2000). Twenty one Bipolar-I patients (10 men, 11 women) were recruited on the basis of the following inclusion criteria: age 18–55 years, *DSM-IV* criteria for remission (i.e., no significant signs or symptoms of the disturbance present during the past 2 months), score <7 on Hamilton Depression (HAMD) and the Young Mania Rating Scales (YMRS) on the testing day, on the same type and dose of medication for the preceding 3 months, and having an unaffected sibling. Exclusion criteria were any comorbid Axis I diagnosis, a family history of schizophrenia, and having had electroconvulsive treatment in the past 12 months. Nineteen unaffected siblings (11 men, 8 women) and 42 healthy comparison participants (23 men, 19 women), age and sex matched to the patient and sibling groups, were also recruited. No individual in these groups had a current Axis I or II disorder or a personal history (or family history for the controls) of mood, psychosis, or schizophrenia spectrum disorders. Additional exclusion criteria applied in all participants were a positive urine toxicology screen, a history of head injury with loss of consciousness, medical conditions (e.g., diabetes, HIV, cancer, hypertension, myocardial infarction), contraindications to individual study investigations (e.g., current treatment with steroids or antihypertensives), presence of a neurological disorder, negligible startle responses (mean amplitude <10 mV) and/or more than two discarded trials per trial type (no participants were excluded on the basis of this criterion). All participants had a hearing threshold of 1 kH >20 dB.

All participants underwent the same diagnostic evaluation. The Structured Clinical Interview (SCID) for *DSM-IV* and the SCID-II Personality Questionnaire were used for Axis I and II diagnoses, respectively (First, Spitzer, Gibbon, & Williams, 1994, 1997). Psychopathology was rated using the HAMD (Hamilton, 1960) and the YMRS (Young, Biggs, Ziegler, & Meyer, 1978), and the Global Assessment of Functioning (GAF; American Psychiatric Association, 2000) was used as a measure of overall function. Family history of psychiatric disorders was assessed in all participants using the Family Interview for Genetic Studies (Maxwell, 1992) supplemented by medical notes as necessary. All instruments were available in the Greek language for use in the Greek population.

Startle Testing

All participants had been instructed to maintain their normal patterns of caffeine and nicotine consumption until the morning of the experimental testing to avoid possible effects of caffeine (Andrews, Blumenthal, & Flaten, 1998) and nicotine withdrawal (Cinciripini et al., 2006) on startle. However, no subject was tested within 10 min of having a cigarette to avoid an effect of nicotine during the testing session. Equipment and setup have been described in detail in our previous studies (Kaviani, Gray, Checkley, Kumari, & Wilson, 1999; Kumari, Cotter, Corr, Gray, & Checkley, 1996; Kumari, Kaviani, Raven, Gray, & Checkley, 2001).

All subjects were presented with 54 pictures (18 pleasant, 18 unpleasant, 18 neutral), each for 6 s, taken from the International Affective Picture System (IAPS; Lang & Bradley, 2005) with some of the pleasant pictures being different for the women and men.[1] Normative arousal ratings (mean $\pm$ *SD*) for the selected IAPS pictures were 5.5 ± 1.3 and 5.1 ± 0.8 for pleasant pictures for men and women, respectively, 2.7 ± 0.5 for neutral pictures, and 6.2 ± 0.7 for unpleasant pictures, thus yielding the usual V pattern in which pleasant and unpleasant pictures are more arousing than neutral ones. Of these, 36 pictures (12/valence type) were accompanied by an acoustic probe (50-ms presentation at 104 dB white noise over 70-dB background noise running throughout the experiment). Of the 12 acoustic probes presented during each affective category, 4 were presented 300 ms after the picture onset, 4 were presented 3000 ms after the picture onset, and 4 probes were presented 4500 ms after the picture onset. There were no differences in normative arousal ratings between pictures accompanied by different types of probes within the same affective category. Six pictures of each valence type were not accompanied with a startle probe (NOSTIM pictures) to increase unpredictability of startle stimuli; normative arousal ratings of the NOSTIM pictures showed a significant effect of valence, $F(3,24) = 15.9$, $p < .001$; neutral $<$ unpleasant = pleasant for men or women. Each picture was followed by a blank screen of the same duration as the affective pictures (6 s). Subjects also received 15 acoustic probes during the blank screens in order to increase unpredictability of startle probes. The NOSTIM pictures and the probed blank screens were used for the calculation and between-group comparison of the basal electromyographic (EMG) signal and the baseline startle, respectively, but did not enter any other analyses. Interpicture interval (in addition to the blank screen) was 3–12 s (average 9 s). The experiment lasted about 35 min. The stimuli (pictures and probes) were presented to all subjects in the same order and with the same intertrial intervals.

Prior to scoring and data analysis, all recordings were screened for spontaneous eyeblink activity. Trials were excluded if excessive EMG activity (>20 digital units = 48.8 μV) was observed during the first 20 ms of recording or when onset latencies (defined by a shift of 10 digital units from the baseline value occurring within 20–85 ms after the onset of the pulse stimulus) and peak latencies (the point of maximal amplitude) differed by more than 95 ms. Based on these criteria, 1.1%, 1.3%, and 1% of trials were rejected in the patient, siblings, and control groups, respectively. Trials with no startle response were scored as zero. Scoring was always performed by the same investigator (S.G.) blind to group. Outcome variables inluded the following:

1. Basal EMG activity (a likely measure of arousal and task engagement; Witvliet & Vrana, 1995) was defined as the mean

[1]IAPS numbers for neutral pictures used in the experiment are 2200, 5500, 5510, 7000, 7002, 7009, 7010, 7020, 7040, 7050, 7060, 7080, 7090, 7100, 7150, 7170, 7175, and 7500; for pleasant pictures: 1610, 1750, 2070, 2080, 2550, 4614, 4650, 5830, 7200, 7280, 7330, 8030, 8080, 8120, and 2040, 2050, 4520, 4532 for women and 2030, 4210, 4180, 4232 for men; for unpleasant pictures: 1030, 1070, 1090, 1111, 2120, 3000, 3010, 3030, 3064, 3100, 3130, 3140, 3150, 3210, 6242, 6570, 9050, and 9405.

EMG activity across the entire picture window in the NOSTIM pictures averaged across the same valence type.
2. Baseline startle magnitude was defined as the mean startle magnitude across all probes during the blank screens.
3. Startle magnitude responses were averaged across the same probe onsets/valence type.
4. Percent prepulse inhibition (%PPI) effects at 300 ms were calculated according to the formula [(baseline startle magnitude (blank trials) − startle magnitude at 300 ms)/baseline startle magnitude (blank trials)] × 100.

Procedure

The clinical assessment and history taking were conducted in the week preceding testing. On the day of testing, subjects rated their subjective mood and feelings using 10-cm visual analogue scales (VAS) on alert–drowsy (drowsiness), calm–tense (anxiety), and happy–sad (discontentment) dimensions before and after startle testing. After startle testing, affective picture ratings (+10 to 0 to −10 scale, with anchor points labeled *extremely pleasant* and *extremely unpleasant*) for each picture were also obtained.

Data Reduction and Analysis

Demographic data (age, years of education, number of smokers) were compared between the groups using either analysis of variance (ANOVA) or Pearson's chi-square. VAS mood ratings before startle testing were compared between the three groups using one-way ANOVA, with post hoc Bonferroni pairwise comparisons, and identical analyses were performed on the pre- and posttesting differences of the VAS data.

Affective picture ratings were analyzed with repeated measures ANOVAs with group (three levels: patients, relatives, controls) as the between-subjects factor and valence (three levels: pleasant, neutral, unpleasant) as the within-subject factor. Basal EMG from the NOSTIM pictures was analyzed with a repeated measures ANOVA with group (three levels) and gender (two levels) as the between-subjects factor and valence (three levels) as the within-subject factor. Mean baseline startle elicited during the blank screens was compared between groups with one-way ANOVA. Startle magnitude was analyzed with repeated measures ANOVA with group (three levels) and gender (two levels) as the between-subjects factor and valence (three levels) and probe onset (two levels: 3000 ms, 4500 ms) as the within-subject factor. Percent PPI at 300 ms was compared with a 3 × 3 × 2 (Valence × Group × Gender) repeated measures ANOVA. All repeated measures with more than two levels (or one degree of freedom) employed the Greenhouse–Geisser epsilon correction. Uncorrected degrees of freedom are reported in this case, with the corrected p values and the epsilon value. Effect sizes (partial eta squared) are also reported.

Startle magnitude was also compared between patient subgroups. Antipsychotic medication dose was converted to chlorpromazine equivalents and clinically equivalent doses, as there is no agreed method for converting the dose of atypical antipsychotics (Bezchlibnyk-Butler & Jeffires, 2000). The potential effect of antipsychotic medication dose and clinical features were controlled with ANCOVA models.

Results

Demographic and Clinical Data

The mean age of patients was 32.71 ± 7.28 years, of the siblings 31.84 ± 7.40 years, and of the controls 35.98 ± 11.01 years. The groups did not differ in age, $F(2,81) = 1.60$ $p > .1$], gender ratio, Pearson $\chi^2(2) = 0.12$, $p > .9$, and smokers:nonsmokers ratio (patients: 12:9; siblings: 11:8; controls: 18:24), Pearson $\chi^2(2) = 1.76$, $p > .4$. The patients had significantly lower GAF scores than sibling and comparison groups (patients: 72.33 ± 9.69; siblings: 88.21 ± 5.99; controls: 87.6 ± 4.3), Kruskal-Wallis $\chi^2(2) = 42.46$, $p < .001$. Table 1 shows the clinical description of the patient group. All the patients were medicated, 18 with either lithium or an anticonvulsant (2 patients were on a combination); 14 patients were also prescribed antipsychotics for their antimanic rather than antipsychotic action, although 9 patients had a history of psychotic symptoms during mood episodes. Details of the medication are also shown in Table 1.

Table 1. *Clinical Characteristics of the Bipolar-I Group*

	Bipolar patients ($n = 21$)
Mean duration of illness (*SD*) in months	112.90 (95.19)
Mean age at onset (*SD*) in years	24.05 (05.51)
Mean number of total episodes	05.35 (04.45)
Mean HAMD total score (*SD*)/range	03.86 (02.63)/(0–7)
Mean YMRS total score (*SD*)/range	03.67 (02.37)/(0–7)
Mean BPRS total score (*SD*)	27.29 (04.99)
Mean GAF score (*SD*)	72.33 (09.69)
% (no.) on antipsychotic medication	66.66 (14)
% (no.) on typical, atypical, combined	33.33 (7), 42.86 (9), 09.52 (2)
Mean antipsychotic dose (*SD*) CPZ equivalents (mg)	416.14 (351.25)
Mean antipsychotic dose (*SD*) clinical equivalents (mg)	330.90 (296.87)
% (no.) on lithium/mean dose (*SD*) (mg)	28.50 (6)/1265 (324.45)
% (no.) on Valproate/mean dose (*SD*) (mg)	19.00 (4)/887 (577.89)
% (no.) on Carbamazepine/mean dose (*SD*) (mg)	48.00 (10)/600.00 (316.23)

HAMD: Hamilton Depression Scale; YMRS: Young Mania Rating Scale; BPRS: Brief Psychiatric Rating Scale; GAF: Global Assessment of Functioning; CPZ: Chlorpromazine.

Affective Picture Ratings

The affective picture ratings for the entire sample (mean ± *SD*) were −6.4 ± 2.5 (unpleasant), 1.9 ± 2.5 (neutral), and 7.2 ± 2.0 (pleasant), and they confirmed the categorization of the pictures as pleasant, neutral, and unpleasant. Table 2 shows that both patient and sibling groups scored the pleasant and neutral pictures more positively and the unpleasant pictures more negatively than controls. A 3 × 3 (Valence × Group) ANOVA showed significant main effects of valence, $F(2,158) = 694.3$, $p < .001$, $\varepsilon = .8$, $\eta^2 = .898$, but not group, $F(2,79) = 2.1$, $p > .1$, $\eta^2 = .05$, and a significant interaction, $F(4,158) = 4.5$, $p < .05$, $\eta^2 = .103$. Follow-up of the interaction with one-way ANOVAs at each valence showed significant group effects at neutral and unpleasant valence, $F(2,79) = 5.1$, $p < .01$ and $F(2,79) = 4.1$, $p < .05$, respectively. Dunnett's tests showed that the patient group scored the neutral pictures more positively than controls ($p < .01$) and the sibling group scored the unpleasant pictures more negatively than controls ($p < .05$).

Mood Ratings on the Visual Analogue on the Day of Testing

Table 2 shows the pre- and posttesting values in the three dimensions of the VAS-rated mood for each group. The groups' VAS ratings did not differ before startle testing in any of the three VAS dimensions, $F_{\text{drowsiness}}(2,81) < 1$, $F_{\text{anxiety}}(2,81) = 2.8$, $p > .06$, $F_{\text{discontentment}}(2,81) < 1$. Separate one-way ANOVAs of

Table 2. *Basal EMG Activity from NOSTIM Trials and VAS-Rated Mood and Affective Picture Ratings in the Three Groups (Mean ± SD)*

	Patients	Relatives	Controls
Basal EMG activity			
Pleasant	47.3 ± 47.8	34.6 ± 17.7	44.9 ± 29.3
Neutral	43.5 ± 41.1	31.4 ± 8.1	43.6 ± 28.0
Unpleasant	45.0 ± 41.4	37.4 ± 20.2	47.9 ± 35.8
Affective picture ratings			
Pleasant	7.8 ± 1.7	7.2 ± 2.0	6.9 ± 2.0
Neutral	3.3 ± 3.0	1.8 ± 2.2	1.2 ± 2.1
Unpleasant	− 6.9 ± 2.6	− 7.4 ± 1.4	− 5.7 ± 2.7
VAS-rated mood at pretest			
Drowsiness	4.00 ± 2.83	4.42 ± 2.02	4.24 ± 2.39
Anxiety	2.74 ± 2.83	4.60 ± 2.59	3.18 ± 2.46
Discontentment	3.88 ± 2.64	3.73 ± 1.94	3.96 ± 2.26
VAS-rated mood at posttest			
Drowsiness	4.05 ± 2.87	4.57 ± 2.13	5.06 ± 2.46
Anxiety	2.65 ± 2.75	4.48 ± 2.74	3.29 ± 2.20
Discontentment	3.91 ± 2.64	3.48 ± 1.83	3.93 ± 2.08

the pre-and posttesting changes in the VAS ratings also did not reveal any significant main effect of group in any of the three dimensions (all p values $> .19$).

Basal EMG Activity

The group means of basal EMG activity for the three groups are shown in Table 2. A 3 × 3 × 2 (Valence × Group × Gender) repeated measures ANOVA of the basal EMG activity data from the NOSTIM trials revealed a significant main effect of valence, $F(2,152) = 3.7$, $p < .05$, $\varepsilon = .944$, $\eta^2 = .046$, with significant quadratic trends, $F(1,76) = 8.9$, $p < .01$, $\eta^2 = .105$, showing that arousal as captured by basal EMG activity during both pleasant and unpleasant picture viewing was greater than that during neutral picture viewing. The Group × Valence interaction was not significant ($F < 1$), suggesting that this pattern did not differ between the groups. All other main effects or interactions were nonsignificant (all p values $> .2$).

Baseline Startle

The mean ± *SD* startle magnitude (in digital units) during the blank screens was 137.9 ± 117.6, 147.7 ± 121.3, and 264.0 ± 186.8 for the patient, sibling, and control groups, respectively. A one-way ANOVA showed a significant difference between the groups, $F(2,81) = 6.1$, $p = .01$, and post hoc Bonferroni tests showed that both patient and sibling groups had lower baseline startle magnitude compared to the control group (p values $< .05$), with medium to large effect sizes (Cohen's $d = 0.74$ and 0.81 for the sibling and the patient groups, respectively). There were no effects of gender or smoking status on baseline startle magnitude, $F(1,81) = 1.9$, $p > .17$ and $F < 1$, respectively.

Affective Startle Modulation[2]

An overall 3 × 2 × 3 × 2 (Valence × Probe Onset × Group × Gender) repeated measures ANOVA showed main effects of valence, trend: $F(2,152) = 2.95$, $p < .06$, $\varepsilon = .867$, $\eta^2 = .037$, and group, $F(2,76) = 6.2$, $p < .01$, $\eta^2 = .140$, and a significant Valence × Group interaction, $F(4,152) = 6.5$, $p < .001$, $\eta^2 = 0.146$. The main effect of gender was significant, $F(1,76) = 4.05$, $p < .05$, $\eta^2 = .051$, with female > male, whereas the remaining effects and interactions were not (all $F < 1$). Because groups differed in baseline startle and in the way they rated the affective pictures (see above), the baseline startle and affective picture ratings for all affective categories were used separately or together as the covariates in ANCOVAs with the identical factorial design. The ANCOVA including all these covariates showed that the main effect of group was no longer significant, $F(1,72) = 2.12$, $p > .1$, $\eta^2 = .056$, the gender and valence main effects remained, $F(1,72) = 4.6$, $p < .05$, $\eta^2 = .06$, and $F(2,144) = 4.95$, $p < .01$, $\varepsilon = .904$, $\eta^2 = .064$, respectively, and the critical Valence × Group interaction also remained significant, $F(4,144) = 7.8$, $p < .001$, $\eta^2 = .177$. The pattern seen in Figure 1 with a significant Valence × Group interaction (at $p < .001$) in the overall ANOVA remained when the control group was limited to (a) subjects selected 1:1 for nearly identical baseline startle (mean ± *SD* = 155.4 ± 26.4) with the patient or the sibling groups or (b) subjects with a lower than median baseline startle, resulting in a group mean of 122.4 (*SD* = 41.1), which was actually lower than that of both patient and sibling groups.

Follow-up of the significant interactions of the overall ANOVA with 3 × 2 (valence × probe onset) repeated measures ANOVAs for each group showed a significant main effect of valence, $F(2,82) = 15.04$, $p < .001$, $\varepsilon = .732$, $\eta^2 = .268$; linear trend: $F(1,41) = 19.86$, $p < .001$, $\eta^2 = .326$, in controls, suggesting significant increases in startle magnitude from pleasant to neutral to unpleasant pictures at 3000-ms and 4500-ms probes (Figure 1, right panel). A significant valence main effect, $F(2,18) = 6.4$, $p < .05$, $\varepsilon = .539$, $\eta^2 = .415$, linear trends, $F(1,9) = 7.6$, $p < .05$, $\eta^2 = .457$, was seen even in the lowest quartile ($n = 10$) of the comparison group with a mean ± *SD* baseline startle magnitude of 84.6 ± 18.1 (61% and 57% of the size of the patients' and siblings' startle, respectively). There were no significant effects in the patient or the sibling groups (Figure 1, left and middle panels), with the greatest effect being a Valence × Probe interaction in the patient group, $F(2,40) = 3.1$, $p < .06$, $\varepsilon = .954$, $\eta^2 = .137$ (all other p values $> .2$).

Comparisons of patients with and without a history of psychosis during mood episodes ($n = 9$ and 12, respectively) and patients with and without past depressive episodes ($n = 16$ and 5, respectively) did not reveal group differences or a significant group involving interaction in startle magnitude (all p values $> .1$). Comparisons of patients with comorbid ($n = 10$) versus no comorbid ($n = 11$) thyroid dysfunction, on antipsychotics ($n = 14$) versus no antipsychotics ($n = 7$), and on lithium ($n = 6$) versus no lithium ($n = 15$) revealed no significant main effects or interactions (all p values $> .07$). Chlorpromazine or clinical equivalents of antipsychotics or lithium dose, age of onset, illness duration, number of episodes, GAF, and symptom ratings did not covary with affective startle modulation in ANCOVA models (all p values $> .1$).

PPI

Percent PPI at 300 ms (mean ± *SD*) was 16.2 ± 39.4 (neutral), 21.2 ± 34.5 (pleasant), and 16.7 ± 32.2 (unpleasant) for the patient group. The same values were 16.9 ± 40.9, 23.8 ± 28.6, and 18.5 ± 23.0 for the sibling group and 31.5 ± 27.5, 39.3 ± 28.8, and 32.4 ± 33.1 for the control group. A 3 × 3 × 2 (Valence × Group × Gender) ANOVA revealed a significant effect of group, $F(2,76) = 3.8$, $p < .05$, $\eta^2 = .092$, and a post hoc

[2]We also tested a group of 19 patients in the United Kingdom, who matched clinically to the Crete sample, and 31 of their relatives and replicated the pattern of effect observed in both patients and relatives group described in this paper.

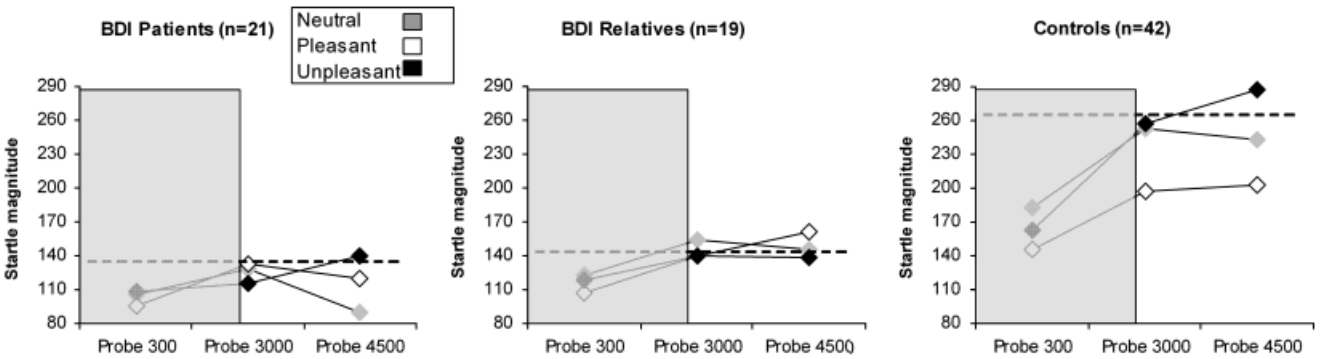

Figure 1. Startle amplitude across pleasant neutral and unpleasant pictures at three probe onset intervals for the three groups. The broken line denotes the level of baseline startle. Early startle modulation (PPI at 300 ms) is not included in the analysis of the late (affective) startle modulation, but it is presented (shaded) for completion of between-group comparison.

Dunnett's test showed that both clinical groups had lower PPI compared to controls ($p < .05$). The main effects of gender and valence and all interactions were not significant (all $F < 1$). Baseline startle did not correlate with %PPI in any of the affective categories in any of the three groups (all p values $> .1$).

Discussion

We found that remitted BD patients and their unaffected siblings had low baseline startle amplitude compared to controls and failed to show the expected attentional startle inhibition by early probes (PPI) or the affective modulation of startle amplitude by valence; their startle response was blunted across both valence and probe latency (Figure 1). The presence of these findings in the unaffected siblings argues against blunted startle reactivity reflecting residual subclinical symptoms, medication, a deficit state, or a neurobiological "scar" resulting from past illness episodes. Instead, our findings suggest that reduced baseline startle and blunted attentional and affective startle modulation are vulnerability traits of BD-I.

The observed group differences in baseline startle between healthy individuals and BD-I patients and their siblings were surprisingly robust (Cohen's $d = 0.81$ and 0.74, respectively). In the absence of perceptual impairments (which are highly improbable here), one can only speculate that the low baseline startle in patients and their siblings reflects reduced baseline excitability within the startle reflex circuitry. Studies on neurological patients have shown that lesions of the amygdala (Angrilli et al., 1996; Buchanan, Tranel, & Adolphs, 2004; Funayama, Grillon, Davis, & Phelps, 2001; Kettle, Andrewes, & Allen, 2006) and the orbitofrontal cortex (Angrilli, Bianchin, Radaelli, Bertagnoni, & Pertile, 2008) dramatically attenuate overall startle reflex magnitude, confirming the involvement of these brain areas in tonic startle reactivity in humans. This possibility warrants further examination; although the current study design does not allow us to measure directly the level of engagement at neural level, it is of note that the above mentioned areas modulating the primary startle circuit overlap significantly with regions implicated in the structural and functional neuroanatomy of BD (Haldane & Frangou, 2004; Strakowski et al., 1999).

Startle attenuation in the early stages of affective picture viewing is an example of PPI that is thought to protect the processing of the (pictorial) prepulse stimulus from the disruptive startle stimulus (Bradley et al., 1993). Healthy individuals in our study showed significant startle attenuation (PPI) at 300 ms during processing of all picture contents relative to baseline startle. BD-I patients and their relatives failed to show the normal early startle attenuation (at 300 ms), thus replicating our previous report of deficient PPI in these groups (Giakoumaki et al., 2007). This finding can be interpreted as evidence of reduced "sensorimotor gating" in BD-I patients and their relatives and resonates with reports of enhanced susceptibility to interference and reduced response inhibition in these groups (Arts, Jabben, Krabbendam, & van Os, 2008; Frangou, Haldane, Roddy, & Kumari, 2005). Animal (Swerdlow, Caine, Braff, & Geyer, 1992; Swerdlow, Geyer, & Braff, 2001) and human neuroimaging studies (Campbell et al., 2007; Kumari, Antonova, et al., 2005; Kumari et al., 2003) implicated the hippocampus, amygdala, nucleus accumbens, dorsal striatum, ventral pallidum, and ventral prefrontal cortex in phasic startle reflex inhibition by a prepulse. It is notable, again, that many of these areas modulating the inhibition of startle by a prepulse overlap with regions implicated in the structural and functional neuroanatomy of BD (Haldane & Frangou, 2004; Strakowski et al., 1999).

As expected, in healthy individuals the effect of valence became more evident at 3000 ms and maximum valence-induced differentiation of startle amplitudes occurred at 4500 ms, suggesting a progressive activation of motivational systems and emotional engagement with affective pictures. Both BD-I patients and their relatives failed to show any modulation of the startle response by valence even at 4500 ms. This is unlikely to reflect inadequate power to detect any modulation had it been present, because valence accounted for 32.6% of the total variance in the healthy group and for less than 8.9% and 4.2% in the patient and relative groups, respectively. We examined and excluded the possibility that factors such as gender, smoking habit, mood state at the time of testing, baseline startle, and basal EMG (a likely measure of arousal and task engagement) could have contributed to the lack of startle modulation. We did not obtain detailed arousal ratings from our participants, which is a limitation of our study, but we selected pictures of equal normative arousal scores, consistent with the majority of the literature. BD-I patients and their siblings, however, had higher ratings for the affective pictures, which indicates that they attributed greater emotional salience to these stimuli. Our finding of blunted affective modulation in BD-I patients in this study is at odds with the report by Forbes et al. (2005) of normal affective modulation in mildly depressed BD-I and BD-II patients. It is possible that trait and state emotional reactivity in BD may be different, and

longitudinal designs will be helpful in interpreting disparities between studies.

It would appear from our startle data that an underactive BAS could be a vulnerability trait in BD and that the emotion-context insensitivity model may best describe trait-related changes in emotional reactivity in BD. However, the classic formulation of this model that proposes disengagement from the environment cannot explain the higher ratings of the emotional pictures by the patients and their relatives. Perhaps an alternative explanation that would be in line with a dysregulated BAS in BD (Urosević et al., 2008) is that remitted BD-I patients and their relatives may attribute greater salience to emotional events, possibly making them susceptible to emotional instability, and that the pattern of effects we observed may represent an adaptive homeostatic response in order to down-regulate their emotion. Attempts to down-regulate emotion have been shown to result in reduced startle reactivity/modulation and skin conductance responses to affective (IAPS) pictures (Driscoll, Tranel, & Anderson, 2009), and this may have occurred in our patient and sibling groups across the entire experiment, given its nature, which was described in advance to all study participants.

The reduced baseline startle and blunted affective startle reactivity observed in BD patients and their siblings are strikingly reminiscent of similar findings in patients with MDD (Allen et al., 1999; Kaviani et al., 2004; O'Brien-Simpson et al., 2009). Importantly, however, the deficient attentional startle modulation (PPI) observed in this and our previous study in BD patients and their relatives (Giakoumaki et al., 2007), although common among schizophrenia patients and their relatives (Cadenhead, Swerdlow, Shafer, Diaz, & Braff, 2000; Kumari, Das, Zachariah, Ettinger, & Sharma, 2005), is absent in MDD patients (Perry, Minassian, & Feifel, 2004; Quednow et al., 2004; Quednow, Westheide, et al., 2006) unless they have a history of psychosis (Perry et al., 2004). Also, existing data, although very limited, suggest that relatives of patients with MDD have higher baseline startle but normal affective modulation (Grillon et al., 2005). In contrast, schizophrenia patients and their relatives show normal affective startle modulation (Curtis, Lebow, Lake, Katsanis, & Iacono, 1999; Schlenker, Cohen, & Hopmann, 1995; Volz, Hamm, Kirsch, & Rey, 2003), with some evidence of reduced baseline startle in untreated patients (Quednow et al., 2008; Quednow, Wagner, et al., 2006).

These emerging differential patterns of deficiencies in startle reactivity and its early (attentional) and late (affective) modulation, studied alongside key clinical (e.g., anxiety, a past history of psychosis) and cognitive features (e.g., response inhibition deficits; Stefanopoulou et al., 2009) may provide a greater understanding of the commorbidity and boundaries between MDD and bipolar and schizophrenia spectrum disorders and facilitate the inception of a biologically more valid typology. Temperaments might represent the underlying dimensions in the overlap of these conditions, along with genetic, developmental, and pathophysiological lines (Akiskal & Akiskal, 2005; Cloninger et al., 1993). It may be relevant here that a dopamine D4 receptor polymorphism (the long DRD4 variable number tandem repeat, L-DRD4 VNTR) that is associated with increased novelty seeking (Ebstein et al., 1996) is also associated with lower startle reactivity and reduced affective but not attentional startle modulation (Roussos et al., 2009). The D4 receptor is highly distributed in prefrontal and limbic areas such as the amygdala and hippocampus relevant to affect regulation (Meador-Woodruff et al., 1996), and the L-DRD4 VNTR polymorphism has been implicated in bipolar disorder (Serretti & Mandelli, 2008). Therefore, the influence of this polymorphism in reduced startle reactivity and reduced affective startle modulation in BD-I should be examined in future studies. Future research should also examine baseline startle and affective startle modulation in Bipolar-I patients and their unaffected first-degree relatives genotyped for dopaminergic gene polymorphisms and assessed for approach/avoidance behaviors (e.g., Cloninger's novelty seeking, harm avoidance, and reward dependence; Cloninger, Adolfsson, & Svrakic, 1996), which are mediated by dopamine release in the nucleus accumbens and the amygdala (Gray, 1987; Gray, Pickering, & Gray, 1994) and reported previously to mediate affective startle modulation in nonclinical populations (Cook et al., 1991; Corr, Kumari, Wilson, Checkley, & Gray, 1997; Kumari et al., 1996). Other relevant polymorphisms may be those affecting the responsivity of the HPA system, the exaggerated activity of which may underlie attenuated startle and mood disorders (see O'Brien-Simpson et al., 2009, for a full discussion).

To our knowledge, this is the first study to examine differences in baseline startle and attentional and affective startle modulation between healthy subjects, remitted bipolar patients, and subjects at high familial risk for Bipolar-I. We conclude that attenuated startle reactivity together with blunted attentional and affective startle modulation may be markers of vulnerability to Bipolar-I. Further studies are required to investigate whether the startle abnormalities found in both bipolar disorder patients and their relatives are associated with a genetic predisposition to the disorder, environmental factors associated with the illness, and/or an interaction between the genetic and environmental factors.

REFERENCES

Akiskal, K. K., & Akiskal, H. S. (2005). The theoretical underpinnings of affective temperaments: Implications for evolutionary foundations of bipolar disorder and human nature. *Journal of Affective Disorders*, *85*, 231–239.

Allen, N. B., Trinder, J., & Brennan, C. (1999). Affective startle modulation in clinical depression: Preliminary findings. *Biological Psychiatry*, *46*, 542–550.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., Text Revision). Washington, DC: American Psychiatric Press.

Andrews, S. E., Blumenthal, T. D., & Flaten, M. A. (1998). Effects of caffeine and caffeine-associated stimuli on the human startle eyeblink reflex. *Pharmacology Biochemistry & Behavior*, *59*, 39–44.

Angrilli, A., Bianchin, M., Radaelli, S., Bertagnoni, G., & Pertile M, . (2008). Reduced startle reflex and aversive noise perception in patients with orbitofrontal cortex lesions. *Neuropsychologia*, *46*, 1179–1184.

Angrilli, A., Mauri, A., Palomba, D., Flor, H., Birbaumer, N., Sartori, G., et al. (1996). Startle reflex and emotion modulation impairment after right amygdala lesion. *Brain*, *119*, 1991–2000.

Anokhin, A. P., Golosheykin, S., & Heath, A. C. (2007). Genetic and environmental influences on emotion-modulated startle reflex: A twin study. *Psychophysiology*, *44*, 106–112.

Anokhin, A. P., Heath, A. C., Myers, E., Ralano, A., & Wood, S. (2003). Genetic influences on prepulse inhibition of startle reflex in humans. *Neuroscience Letters*, *353*, 45–48.

Arts, B., Jabben, N., Krabbendam, L., & van Os, J. (2008). Meta-analyses of cognitive functioning in euthymic bipolar patients and their first-degree relatives. *Psychological Medicine*, *38*, 771–785.

Beck, D. A., & Koenig, H. G. (1965). Minor depression: A review of the literature. *International Journal of Psychiatry in Medicine*, *26*, 177–209.

Benning, S. D., Patrick, C. J., & Iacono, W. G. (2005). Psychopathy, startle blink modulation, and electrodermal reactivity in twin men. *Psychophysiology*, *42*, 753–762.

Bezchlibnyk-Butler, K. Z., & Jeffires, J. J. (2000). *Clinical handbook of psychotropic drugs*. Toronto, Ontario, Canada: Hogrefe & Huber Publishers.

Bouchard, T. J., & McGue, M. (2003). Genetic and environmental influences on human psychological differences. *Journal of Neurobiology*, *54*, 4–45.

Bradley, M. M., Cuthbert, B. N., & Lang, P. J. (1990). Startle reflex modification: Emotion or attention? *Psychophysiology*, *27*, 513–522.

Bradley, M. M., Cuthbert, B. N., & Lang, P. J. (1993). Pictures as prepulse: Attention and emotion in startle modification. *Psychophysiology*, *30*, 541–545.

Bradley, M. M., Cuthbert, B. N., & Lang, P. J. (1999). Affect and the startle reflex. In N. Birbaumer & A. Ohman (Eds.), *The structure of emotion*. Bern, Switzerland: Hogrefe and Huber.

Buchanan, T. W., Tranel, D., & Adolphs, R. (2004). Anteromedial temporal lobe damage blocks startle modulation by fear and disgust. *Behavioral Neuroscience*, *118*, 429–437.

Cadenhead, K. S., Swerdlow, N. R., Shafer, K. M., Diaz, M., & Braff, D. L. (2000). Modulation of the startle response and startle laterality in relatives of schizophrenic patients and in subjects with schizotypal personality disorder: Evidence of inhibitory deficits. *American Journal of Psychiatry*, *157*, 1660–1668.

Campbell, L. E., Hughes, M., Budd, T. W., Cooper, G., Fulham, W. R., Karayanidis, F., et al. (2007). Primary and secondary neural networks of auditory prepulse inhibition: A functional magnetic resonance imaging study of sensorimotor gating of the human acoustic startle response. *European Journal of Neuroscience*, *26*, 2327–2333.

Carlson, S. R., Katsanis, J., Iacono, W. G., & McGue, M. (1997). Emotional modulation of the startle reflex in twins: Preliminary findings. *Biological Psychology*, *46*, 235–246.

Cinciripini, P. M., Robinson, J. D., Carter, B. L., Lam, C., Wu, X., de Moor, C. A., et al. (2006). The effects of smoking deprivation and nicotine administration on emotional reactivity. *Nicotine and Tobacco Research*, *8*, 379–392.

Cloninger, C. R., Adolfsson, R., & Svrakic, N. M. (1996). Mapping genes for human personality. *Nature Genetics*, *12*, 3–4.

Cloninger, C. R., Svrakic, D. M., & Przybeck, T. R. (1993). A psychobiological model of temperament and character. *Archives of General Psychiatry*, *50*, 975–990.

Cook, E. W., Davis, T. L., Hawk, L. W., Spence, E. L., & Gautier, C. H. (1992). Fearfulness and startle potentiation during aversive visual stimuli. *Psychophysiology*, *29*, 633–645.

Cook, E. W., Hawk, L. W., Davis, T. L., & Stevenson, V. E. (1991). Affective individual differences and startle reflex modulation. *Journal of Anormal Psychology*, *100*, 5–13.

Corr, P. J., Kumari, V., Wilson, G. D., Checkley, S., & Gray, J. A. (1997). Harm avoidance and affective modulation of the startle reflex: A replication. *Personality and Individual Differences*, *22*, 591–593.

Curtis, C. E., Lebow, B., Lake, D. S., Katsanis, J., & Iacono, W. G. (1999). Acoustic startle reflex in schizophrenia patients and their first-degree relatives: Evidence of normal emotional modulation. *Psychophysiology*, *36*, 469–475.

Depue, R. A., & Iacono, W. G. (1989). Neurobehavioral aspects of affective disorders. *Annual Review of Psychology*, *40*, 457–492.

Depue, R. A., Krauss, S., & Spoont, M. R. (1987). A two-dimensional threshold model of seasonal bipolar affective disorder. In D. Magnusson & A. Ohman (Eds.), *Psychopathology: An interactionist perspective* (pp. 95–123). New York: Academic Press.

Dichter, G. S., & Tomarken, A. J. (2008). The chronometry of affective startle modulation in unipolar depression. *Journal of Abnormal Psychology*, *117*, 1–15.

Dichter, G. S., Tomarken, A. J., Shelton, R. C., & Sutton, S. K. (2004). Early- and late-onset startle modulation in unipolar depression. *Psychophysiology*, *41*, 433–440.

Driscoll, D., Tranel, D., & Anderson, S. W. (2009). The effects of voluntary regulation of positive and negative emotion on psychophysiological responsiveness. *International Journal of Psychophysiology*, *72*, 61–66.

Ebstein, R. P., Novick, O., Umansky, R., Priel, B., Osher, Y., Blaine, D., et al. (1996). Dopamine D4 receptor (D4DR) exon III polymorphism associated with the human personality trait of novelty seeking. *Nature Genetics*, *12*, 78–80.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (1994). *Structured Clinical Interview for Axis I DSM-IV Disorders-Patient Edition (SCID-I/P), Version 2.0*. New York: Psychiatric Research Institute.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (1997). *Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II)*. Washington, DC: American Psychiatric Press.

Forbes, E. E., Miller, A., Cohn, J. F., Fox, N. A., & Kovacs, M. (2005). Affect-modulated startle in adults with childhood-onset depression: Relations to bipolar course and number of lifetime depressive episodes. *Psychiatry Research*, *134*, 11–25.

Fowles, D. C. (1988). Psychophysiology and psychopathology: A motivational approach. *Psychophysiology*, *25*, 373–391.

Fowles, D. C. (1993). Biological variables in psychopathology: A psychobiological perspective. In P. B. Sutker & H. E. Adams (Eds.), *Comprehensive handbook of psychopathology* (2nd ed., pp. 57–82). New York: Plenum Press.

Frangou, S., Haldane, M., Roddy, D., & Kumari, V. (2005). Evidence for deficit in tasks of ventral, but not dorsal, prefrontal executive function as an endophenotypic marker for bipolar disorder. *Biological Psychiatry*, *58*, 838–839.

Funayama, E. S., Grillon, C., Davis, M., & Phelps, E. A. (2001). A double dissociation in the affective modulation of startle in humans: Effects of unilateral temporal lobectomy. *Journal of Cognitive Neuroscience*, *13*, 721–729.

Giakoumaki, S. G., Roussos, P., Rogdaki, M., Karli, C., Bitsios, P., & Frangou, S. (2007). Evidence of disrupted prepulse inhibition in unaffected siblings of bipolar disorder patients. *Biological Psychiatry*, *62*, 1418–1422.

Goodwin, F. K., & Jamison, K. R. (2007). *Manic-depressive illness: Bipolar disorders and recurrent depression* (2nd ed). New York: Oxford University Press.

Gray, J. A. (1982). *The neuropsychology of anxiety: An enquiry into the functions of the septohippocampal system*. Oxford: Oxford University Press.

Gray, J. A. (1987). *The psychology of fear and stress*. Cambridge, UK: Cambridge University Press.

Gray, J. A. (1991). Neural systems, emotion and personality. In J. Madden (Ed.), *Neurobiology of learning, emotion and affect* (pp. 273–306). New York: Raven Press.

Gray, J. A. (1994). Framework for a taxonomy of psychiatric disorder. In S. H. M. van Goozen, N. E. van de Poll, & J. Sergeant (Eds.), *Emotions: Essays on emotion theory* (pp. 29–59). Hillsdale, NJ: Erlbaum.

Gray, N. S., Pickering, A. D., & Gray J, . A. (1994). Psychoticism and dopamine D2 binding in the basal ganglia using single photon emission tomography. *Personality and Individual Differences*, *17*, 431–434.

Grillon, C. (2002). Startle reactivity and anxiety disorders: Aversive conditioning, context and neurobiology. *Biological Psychiatry*, *52*, 958–975.

Grillon, C., & Baas, J. (2003). A review of the modulation of the startle reflex by affective states and its application in psychiatry. *Clinical Neurophysiology*, *114*, 1557–1579.

Grillon, C., Warner, V., Hille, J., Merikangas, K. R., Bruder, G. E., Tenke, C. E., et al. (2005). Families at high and low risk for depression: A three-generation startle study. *Biological Psychiatry*, *57*, 953–960.

Haldane, M., & Frangou, S. (2004). New insights help define the pathophysiology of bipolar affective disorder: Neuroimaging and neuropathology findings. *Progress in Neuropsychopharmacol & Biological Psychiatry*, *28*, 943–960.

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry*, *23*, 56–62.

Hamm, A. O., & Vaitl, D. (1996). Affective learning: Awareness and aversion. *Psychophysiology*, *33*, 698–710.

Haro, G., Calíbrese, J. R., Larsson, C., Shirley, E. R., Martín, E., Leal, C., & Delgado, P. L. (2007). The relationship of personality traits to substance abuse in patients with bipolar disorder. *European Psychiatry*, *22*, 305–308.

Hawk, L. W., & Kowmas, A. D. (2003). Affective modulation and prepulse inhibition of startle among undergraduates high and low in behavioral inhibition and approach. *Psychophysiology*, *40*, 131–138.

Kaviani, H., Gray, J. A., Checkley, S. A., Kumari, V., & Wilson, G. D. (1999). Modulation of the acoustic startle reflex by emotionally-toned film-clips. *International Journal of Psychophysiology*, *32*, 47–54.

Kaviani, H., Gray, J. A., Checkley, S. A., Raven, P. W., Wilson, G. D., & Kumari V. (2004). Affective modulation of the startle response in depression: Influence of the severity of depression, anhedonia, and anxiety. *Journal of Affective Disorders*, *83*, 21–31.

Kesebir, S., Vahip, S., Akdeniz, F., Yüncü, Z., Alkan, M., & Akiskal, H. (2005). Affective temperaments as measured by TEMPS-A in patients with bipolar I disorder and their first-degree relatives: A controlled study. *Journal of Affective Disorders*, *85*, 127–133.

Kettle, J. W. L., Andrewes, D. G., & Allen, N. B. (2006). Lateralization of the startle reflex circuit in humans: An examination with monaural probes following unilateral temporal lobe resection. *Behavioral Neuroscience*, *120*, 24–39.

Kumari, V., Antonova, E., Zachariah, E., Galea, A., Aasen, I., Ettinger, U., et al. (2005). Structural brain correlates of prepulse inhibition of the acoustic startle response in healthy humans. *NeuroImage*, *26*, 1052–1058.

Kumari, V., Cotter, P., Corr, P. J., Gray, J. A., & Checkley, S. A. (1996). Effect of clonidine on the human acoustic startle reflex. *Psychopharmacology*, *123*, 353–360.

Kumari, V., Das, M., Zachariah, E., Ettinger, U., & Sharma, T. (2005). Reduced prepulse inhibition in unaffected siblings of schizophrenia patients. *Psychophysiology*, *42*, 588–594.

Kumari, V., Gray, J. A., Geyer, M. A., Ffytche, D., Soni, W., et al. (2003). Neural correlates of tactile prepulse inhibition: A functional MRI study in normal and schizophrenic subjects. *Psychiatry Research*, *122*, 99–113.

Kumari, V., Kaviani, H., Raven, P. W., Gray, J. A., & Checkley, S. A. (2001). Enhanced startle reactions to acoustic stimuli in patients with obsessive-compulsive disorder. *American Journal of Psychiatry*, *158*, 134–136.

Lang, P. J. (1995). The emotion probe: Studies of motivation and attention. *American Psychologist*, *50*, 372–385.

Lang, P. J., & Bradley, M. M. (2005). *International affective picture system (IAPS): Affective ratings of pictures and instruction manual*. Technical Report A-6. Gainesville, FL: University of Florida.

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1990). Emotion, attention, and the startle reflex. *Psychological Review*, *97*, 377–395.

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1997). Motivated attention: Affect, activation and action. In P. J. Lang, R. F. Simons, & M. T. Balaban (Eds.), *Attention and orienting: Sensory and motivational processes* (pp. 97–113). Hillsdale, NJ: Erlbaum.

Lang, P. J., & Davis, M. (2006). Emotion, motivation, and the brain: Reflex foundations in animal and human research. *Progress in Brain Research*, *156*, 3–29.

Maxwell, M. E. (1992). *Manual for the FIGS*. Bethesda, MD: National Institute of Mental Health.

Meador-Woodruff, J. H., Damask, S. P., Wang, J., Haroutunian, V., Davis, K. L., & Watson, S. J. (1996). Dopamine receptor mRNA expression in human striatum and neocortex. *Neuropsychopharmacology*, *15*, 17–29.

Mendlowicz, M. V., Jean-Louis, G., Kelsoe, J. R., & Akiskal, H. S. (2005). A comparison of recovered bipolar patients, healthy relatives of bipolar probands, and normal controls using the short TEMPS-A. *Journal of Affective Disorders*, *85*, 147–151.

Nery, F. G., Hatch, J. P., Glahn, D. C., Nicoletti, M. A., Monkul, E. S., Najt, P., et al. (2008). Temperament and character traits in patients with bipolar disorder and associations with comorbid alcoholism or anxiety disorders. *Journal of Psychiatric Research*, *42*, 569–577.

O'Brien-Simpson, L., Di Parsia, P., Simmons, J. G., & Allen, N. B. (2009). Recurrence of major depressive disorder is predicted by inhibited startle magnitude while recovered. *Journal of Affective Disorders*, *112*, 243–249.

Olvera, R. L., Fonseca, M., Caetano, S. C., Hatch, J. P., Hunter, K., Nicoletti, M., et al. (2009). Assessment of personality dimensions in children and adolescents with bipolar disorder using the Junior Temperament and Character Inventory. *Journal of Child and Adolescent Psychopharmacology*, *19*, 13–21.

Panksepp, J. (1998). *Affective neuroscience: The foundations of human and animal emotions*. Oxford: Oxford University Press.

Patrick, C. J., Bradley, M. M., & Lang, P. J. (1993). Emotion in the criminal psychopath: Startle reflex modulation. *Journal of Abnormal Psychology*, *102*, 82–92.

Perry, W., Minassian, A., & Feifel, D. (2004). Prepulse inhibition in patients with non-psychotic major depressive disorder. *Journal of Affective Disorders*, *81*, 179–184.

Quednow, B. B., Frommann, I., Berning, J., Kühn, K. U., Maier, W., & Wagner, M. (2008). Impaired sensorimotor gating of the acoustic startle response in the prodrome of schizophrenia. *Biological Psychiatry*, *64*, 766–773.

Quednow, B. B., Kühn, K. U., Stelzenmuelle, R., Hoenig, K., Maier, W., & Wagner, M. (2004). Effects of serotonergic and noradrenergic antidepressants on auditory startle response in patients with major depression. *Psychopharmacology*, *175*, 399–406.

Quednow, B. B., Wagner, M., Westheide, J., Beckmann, K., Bliesener, N., Maier, W., & Kühn, K. U. (2006). Sensorimotor gating and habituation of the startle response in schizophrenic patients randomly treated with amisulpride or olanzapine. *Biological Psychiatry*, *59*, 536–545.

Quednow, B. B., Westheide, J., Kühn, K. U., Werner, P., Maier, W., Hawellek, B., et al. (2006). Normal prepulse inhibition and habituation of acoustic startle response in suicidal depressive patients without psychotic symptoms. *Journal of Affective Disorders*, *92*, 299–303.

Rottenberg, J., & Gotlib, I. H. (2004). Socioemotional functioning in depression. In M. Power (Ed.), *Mood disorders: A handbook of science and practice* (pp. 61–77). New York: Wiley.

Rottenberg, J., Gross, J. J., & Gotlib, I. H. (2005). Emotion context insensitivity in major depressive disorder. *Journal of Abnormal Psychology*, *114*, 627–639.

Rottenberg, J., Kasch, K. L., Gross, J. J., & Gotlib, I. H. (2002). Sadness and amusement reactivity differentially predict concurrent and prospective functioning in major depressive disorder. *Emotion*, *2*, 135–146.

Roussos, P., Giakoumaki, S. G., & Bitsios, P. (2009). Cognitive and emotional processing in high novelty seeking associated with the L-DRD4 genotype. *Neuropsychologia*, *47*, 1654–1659.

Schlenker, R., Cohen, R., & Hopmann, G. (1995). Affective modulation of the startle reflex in schizophrenic patients. *European Archives of Psychiatry and Clinical Neuroscience*, *245*, 309–318.

Serretti, A., & Mandelli, L. (2008). The genetics of bipolar disorder: Genome 'hot regions,' genes, new potential candidates and future directions. *Molecular Psychiatry*, *13*, 742–771.

Shih, R. A., Belmonte, P. L., & Zandi, P. P. (2004). A review of the evidence from family, twin and adoption studies for a genetic contribution to adult psychiatric disorders. *International Review of Psychiatry*, *16*, 260–283.

Sloan, D. M., Strauss, M. E., & Wisner, K. L. (2001). Diminished response to pleasant stimuli by depressed women. *Journal of Abnormal Psychology*, *110*, 488–493.

Stefanopoulou, E., Manoharan, A., Landau, S., Geddes, J. R., Goodwin, G., & Frangou, S. (2009). Cognitive functioning in patients with affective disorders and schizophrenia: A meta-analysis. *International Review of Psychiatry*, *21*, 336–356.

Strakowski, S. M., DelBello, M. P., Sax, K. W., Zimmerman, M. E., Shear, P. K., Hawkins, J. M., et al. (1999). Brain magnetic resonance imaging of structural abnormalities in bipolar disorder. *Archives of General Psychiatry*, *56*, 254–260.

Swerdlow, N. R., Caine, S. B., Braff, D. L., & Geyer, M. A. (1992). Neural substrates of sensorimotor gating of the startle reflex: A review of recent findings and their implications. *Journal of Psychopharmacology*, *6*, 176–190.

Swerdlow, N. R., Geyer, M. A., & Braff, D. L. (2001). Neural circuit regulation of prepulse inhibition of startle in the rat: Current knowledge and future challenges. *Psychopharmacology*, *156*, 194–215.

Tillman, R., Geller, B., Craney, J. L., Bolhofner, K., Williams, M., Zimerman, B., et al. (2003). Temperament and character factors in a prepubertal and early adolescent bipolar disorder phenotype compared to attention deficit hyperactive and normal controls. *Journal of Child and Adolescent Psychopharmacology*, *13*, 531–543.

Urosević, S., Abramson, L. Y., Harmon-Jones, E., & Alloy, L. B. (2008). Dysregulation of the behavioral approach system (BAS) in bipolar spectrum disorders: Review of theory and evidence. *Clinical Psychology Review*, *28*, 1188–1205.

Vaidyanathan, U., Patrick, C. J., & Bernat, E. M. (2009). Startle reflex potentiation during aversive picture viewing as an indicator of trait fear. *Psychophysiology*, *46*, 75–85.

Vázquez, G. H., Kahn, C., Schiavo, C. E., Goldchluk, A., Herbst, L., Piccione, M., et al. (2008). Bipolar disorders and affective temperaments: A national family study testing the "endophenotype" and "subaffective" theses using the TEMPS-A Buenos Aires. *Journal of Affective Disorders*, *108*, 25–32.

Volz, M., Hamm, A. O., Kirsch, P., & Rey, E. R. (2003). Temporal course of emotional startle modulation in schizophrenia patients. *International Journal of Psychophysiology*, *49*, 123–137.

Vrana, S. R., Spence, E. L., & Lang, P. J. (1988). The startle probe response: A new measure of emotion? *Journal of Abnormal Psychology*, *97*, 487–491.

Witvliet, C. V., & Vrana, S. R. (1995). Psychophysiological responses as indices of affective dimensions. *Psychophysiology*, *32*, 436–443.

Young, L. T., Bagby, R. M., Cooke, R. G., Parker, J. D., Levitt, A. J., & Joffe, R. T. (1995). A comparison of Tridimensional Personality Questionnaire dimensions in bipolar disorder and unipolar depression. *Psychiatry Research*, *58*, 139–143.

Young, R. C., Biggs, J. T., Ziegler, V. E., & Meyer, D. A. (1978). A rating scale for mania: Reliability, validity and sensitivity. *British Journal of Psychiatry*, *133*, 429–435.

(Received October 29, 2008; Accepted August 21, 2009)