Published in final edited form as:
J Abnorm Psychol. 2013 August ; 122(3): 662–671. doi:10.1037/a0033982.

Biomarkers of Threat and Reward Sensitivity Demonstrate Unique Associations with Risk for Psychopathology

Brady D. Nelson, **Sarah Kate McGowan**, **Casey Sarapas**, **E. Jenna Robison-Andrew**, **Sarah E. Altman**, **Miranda L. Campbell**, **Stephanie M. Gorka**, **Andrea C. Katz**, and **Stewart A. Shankman**
University of Illinois–Chicago

Abstract

Two emotional/motivational constructs that have been posited to underlie anxiety and depressive disorders are heightened sensitivity to threat and reduced sensitivity to reward, respectively. It is unclear, though, whether these constructs are only epiphenomena or also connote risk for these disorders (and relatedly, whether they connote risk for separate disorders). Using family history of psychopathology as an indicator of risk, the present study examined whether biomarkers of sensitivity to threat (startle potentiation) and reward (frontal EEG asymmetry) were associated with similar or different familial liabilities. In addition, the present study examined whether these biomarkers were associated with risk *independent* of proband DSM-IV diagnosis. One hundred seventy-three individuals diagnosed with panic disorder (PD), early-onset major depressive disorder (MDD), both (comorbids), or controls completed two laboratory paradigms assessing sensitivity to predictable/unpredictable threat (measured via startle response) and reward (measured via frontal EEG asymmetry during a gambling task). Results indicated that across all participants: 1) startle potentiation to unpredictable threat was associated with family history of PD (but not MDD) and 2) frontal EEG asymmetry while anticipating reward was associated with family history of MDD (but not PD). Additionally, both measures continued to be associated with family history of psychopathology after controlling for proband DSM-IV diagnosis. Results suggest that the proposed biomarkers of sensitivity to unpredictable threat and reward exhibit discriminant validity and may add to the predictive validity of the DSM-IV defined constructs of PD and MDD, respectively.

Keywords

anxiety; depression; biomarkers; startle; electroencephalography

In the past decade, research has sought to identify biomarkers (i.e., objective biological indicators of normal or disease processes) of depressive and anxiety disorders to aid in diagnosis, prevention, and treatment efforts (Biomarkers Definitions Working Group, 2001; Hyman, 2007). Biomarkers have the potential to improve understanding of disease etiology and pathophysiology (Schmidt, Shelton, & Duman, 2011). In addition, the inclusion of biomarkers in psychiatric nomenclature would not only allow for less reliance on clinical

Correspondence concerning this article should be addressed to Stewart Shankman, Department of Psychology, University of Illinois-Chicago, 1007 W. Harrison St., Chicago, IL, 60607. stewarts@uic.edu.

presentation, but also help identify objective measures that are associated with *risk* for the disorder.

One way of determining whether biomarkers are associated with risk for psychopathology is through the family study method (Robins & Guze, 1970). Family studies are useful in this context as they can help determine whether a biomarker is associated with a family history of psychopathology (i.e., familial risk). Family studies can also help elucidate the discriminant validity of multiple biomarkers as they can, for example, demonstrate whether biomarker A is associated with risk for different disorders than biomarker B (and vice versa). Two emotional/motivational constructs that have been posited to underlie anxiety and depression (as well as other psychopathologies) and have well-established biological correlates are heightened sensitivity to threat and reduced sensitivity to reward, respectively.[1]

Heightened Sensitivity to Threat as a Mechanism of Anxiety

Several researchers have posited that emotional responses to threat are heterogeneous and the *predictability* of the threatening stimulus makes a difference. Specifically, it has been suggested that fear is elicited by a predictable threat and anxiety is elicited by an unpredictable threat (Grillon et al., 2008; Davis, 2006). This distinction between anxiety and fear has been supported by numerous animal (Davis, 2006), psychophysiological (Grillon et al. 2008), and pharmacological studies (Grillon et al., 2006).

The distinction between fear and anxiety is especially relevant for panic disorder (PD), which is characterized by periods of intense fear (i.e., panic attacks) and anxiety (i.e., anxious apprehension). In separate investigations, Grillon et al. (2008) and Shankman et al. (2013) found that individuals with PD exhibited heightened startle responding while anticipating unpredictable threat. These two studies differed, however, on whether PD was also associated with heightened responding to predictable threat, with Grillon et al. showing no group differences and Shankman et al. showing group differences. Thus, while PD appears to be robustly associated with abnormal response to unpredictable threat (see also Melzig, Weike, Zimmermann, & Hamm, 2007), the findings are more mixed for predictable threat.

Reduced Sensitivity to Reward as a Mechanisms of Depression

A reduced sensitivity to reward has long been argued to be a core feature of depression (Meehl, 1975). One purported biomarker of low reward sensitivity in individuals with depression is an asymmetry in electroencephalogram (EEG) activity between the left and right frontal brain regions (i.e., reduced left relative to right; Davidson, Pizzagalli, Nitschke, & Putnam, 2002). Compared to controls, numerous studies have found reduced left relative to right frontal EEG asymmetries in individuals who are at risk for depression (Tomarken, Dichter, Garber, & Simien, 2004), currently experiencing depression (Thibodeau, Jorgensen, & Kim, 2006), and in remission from depression (Gotlib, Ranganath, & Rosenfeld, 1998; Stewart, Bismark, Towers, Coan, & Allen, 2010). However, most of these investigations examined EEG asymmetry during an uncontrolled ‘resting’ state and not during an actual reward manipulation. Interestingly, Coan, Allen, and McKnight (2006) compared EEG asymmetry during both ‘resting’ and ‘emotional challenge’ conditions, and found that the ‘emotional challenge’ condition was associated with more pronounced individual

[1]The present study focused primarily on internalizing psychopathology as internalizing and externalizing psychopathology have been shown to represent separable (albeit correlated) latent constructs (Kendler, Prescott, Myers, & Neale, 2003; Krueger, 1999). Additionally, it is unclear whether these dimensions play the same role for internalizing vs. externalizing disorders in terms of their association with risk and therefore warrant separate study.

differences, resistance to undesirable variance from reference scheme, and reliable relationships with criterion measures.

Therefore, a superior approach may be to measure frontal EEG asymmetry while manipulating reward (i.e., approach) motivation. To address this issue, Shankman et al. (2007) examined the frontal EEG asymmetry of depressed and control participants while they played a slot machine game designed to elicit approach motivation. Results indicated that adults with childhood or adolescent (i.e., early) onset depression exhibited an abnormal frontal EEG asymmetry compared to controls and adult-onset depressives, who did not differ. Additionally, all three groups did not differ during a 'resting' condition. Other studies have found similar results using different approach motivation manipulations (Stewart, Coan, Towers, & Allen, 2011); although studies are mixed as to which particular form(s) of depression (e.g., early-onset) are associated with the EEG asymmetry biomarker. Taken together, research suggests that abnormal frontal EEG asymmetry may be a potential biomarker for reduced reward sensitivity in depression, or at least certain forms of depression (Stewart et al., 2010).

Present Study

The present study examined whether individual differences on biomarkers of sensitivity to threat (measured via startle potentiation) and reward (measured via frontal EEG asymmetry) were associated with an indicator of risk - family history of psychopathology - in a sample of individuals with PD and/or early-onset major depressive disorder (MDD) and healthy controls. The present study focused on PD and early-onset MDD for several reasons. First, phenotypic and genotypic studies have shown that internalizing psychopathologies can be grouped into two broad factors labeled 'anxious misery' (e.g., depression, dysthymia, and generalized anxiety disorder [GAD]) and 'fear' disorders (e.g., PD, agoraphobia, social phobia, and simple phobia) (Kendler et al., 2003; Kruger, 1999; Watson, 2005). Thus, given the interest in identifying biomarkers that distinguish depression and anxiety disorders, the present study focused on PD (a 'fear' disorder) as opposed to disorders such as GAD (an 'anxious-misery' disorder) given the substantial overlap in etiology and symptom structure between depression and GAD. Second, amongst the 'fear' disorders, PD has the strongest literature showing an association with heightened sensitivity to threat (Grillon et al., 2008; Shankman et al., 2013). Finally, the present study focused on early-onset MDD because Shankman and colleagues (2007) found that participants with early-(but not adult) onset MDD exhibited an abnormal frontal EEG asymmetry relative to controls.

The present study had two additional aims. First, substantial research has found elevated rates of PD in the families of probands with PD (Hettema, Neale, & Kendler, 2001) and elevated rates of depression in the families of probands with depression (Klein, Lewinsohn, Seeley, & Rohde, 2001). Thus, if biomarkers for threat and reward sensitivity were associated with family history of PD and MDD, respectively, it could be due to the shared variance between the biomarker and proband diagnosis and not the unique variance associated with the biomarker. The second aim of this study was therefore to determine whether biomarkers for sensitivity to threat and reward provide incremental validity *independent* of DSM-IV diagnoses in their association with familial risk. This was accomplished by examining whether the association between threat and reward sensitivity and family history of psychopathology remained significant after controlling for proband DSM-IV diagnosis.

A final aim of the study was to examine the discriminant validity of heightened sensitivity to threat and reduced sensitivity to reward. Several theoretical models argue that low sensitivity to reward is uniquely associated with depression (but not anxiety), and high

sensitivity to threat is uniquely associated with anxiety (but not depression) (Clark, Watson, & Mineka, 1994; Shankman & Klein, 2003). Thus, we hypothesized that sensitivity to threat would be uniquely associated with family history of PD (and not MDD), and sensitivity to reward would be uniquely associated with family history of MDD (and not PD). To further examine the discriminant validity of these associations, we also examined family history of alcohol use disorder.

Method

Participants

The sample for the present study was taken from Shankman et al. (2013), and consisted of 191 individuals with current PD and no lifetime diagnosis of any depressive disorder (i.e., PD only), current MDD and no lifetime diagnosis of any anxiety disorder (i.e., MDD only), current PD and current MDD (i.e., comorbids) and controls without a history of Axis I psychopathology. From those 191 participants, 173 provided information on family history of psychopathology in first-degree relatives, leaving a final sample of 26 PD only, 32 MDD only, 54 comorbid, and 61 control participants. Proband diagnosis was examined as two 2-level factors, Depression Status (Present vs. Absent) and Panic Status (Present vs. Absent), instead of one 4-level factor in order to examine main effects and interactions of proband MDD and PD on the variables of interest.

Participants were excluded from the study if they had a lifetime diagnosis of psychosis, bipolar disorder, or dementia; were unable to read or write English; had a history of head trauma with loss of consciousness; or were left-handed (as confirmed by the Edinburgh Inventory; range of laterality quotient: +20 to +100; Oldfield, 1971). Participants were recruited through clinics in the greater Chicago area and advertising in the community.

Proband Diagnosis and Symptomatology Measures

All diagnoses were made via the Structured Clinical Interview for *DSM-IV-TR* (SCID; First, Spitzer, Gibbon, & Williams, 2002). Depression severity was determined via the 24-item Hamilton Depression Scale (HAM-D; Hamilton, 1960). Anxiety severity was determined via the Beck Anxiety Inventory (BAI; Beck, Epstein, Brown, & Steer, 1988). Eight participants (3 controls, 2 MDD only, 2 PD only, and 1 comorbid) did not complete the BAI.

Both depressed groups were required to have an age of onset of first affective disorder (dysthymia or MDD) before age 18 as discussed above. This inclusion criterion reduced the heterogeneity in the MDD groups (Klein, 2008). Participants in the PD only and comorbid groups were allowed to meet criteria for additional current and past anxiety disorders. Additional current anxiety disorders included social phobia ($n = 14$), specific phobia ($n = 11$), posttraumatic stress disorder ($n = 9$), and obsessive-compulsive disorder ($n = 6$). Comorbid (63.0%) and PD only (46.2%) participants did not differ in the rate of other current anxiety disorders, $\chi^2(1, N = 80) = 2.03$, *ns*. Control participants were required to have no lifetime history of Axis I psychopathology, with the exception of a past diagnosis of alcohol or cannabis abuse (but not dependence, $n = 3$). Control participants were also required to have HAM-D and BAI scores less than 8.

Family History

After completing the diagnosis and symptomatology measures, family history of psychopathology was assessed by the same interviewer using the Family History Screen (FHS; Weissman et al., 2000). The FHS is a fully-structured interview that collects information on the lifetime history of 15 psychiatric disorders and suicide attempts in first-

degree relatives. The present study focused on family history of PD, depression, and alcohol use disorder, given the diagnostic composition of the proband groups. The interviewer asked the proband a screening question pertaining to whether any first-degree relative had ever experienced core symptoms of the disorder during their lifetime (e.g., "sad, blue, or depressed mood" for depression). The interviewer then asked a second question regarding those family members' impairment, duration, and/or exclusion criteria (e.g., "not mourning" for depression). A proband was considered to have a family history of a disorder if they had at least one relative who passed the initial screening question *and* the impairment, duration, and/or exclusion question. The FHS has yielded acceptable test-retest reliability and validity when compared to direct interviews (Weissman et al., 2000).

Procedure

Participants completed the following experimental tasks designed to measure sensitivity to threat (No Threat, Predictable Threat, Unpredictable Threat [NPU]-startle task) and reward (slot EEG task). The two tasks were presented in a counterbalanced order, which did not differ between groups. For both tasks, participants were seated in an electrically shielded, sound-attenuated booth approximately 3.5-feet from a 19-inch computer monitor. Task main effects and proband group differences in psychophysiological and verbal responding to the tasks are presented in Shankman et al. (2013).

NPU-Startle Task and Physiological Recordings—To prevent early-exaggerated startle responding, participants were presented with 9 acoustic startle probes over a 2.5-min baseline period prior to the NPU-startle task. Next, a shock work-up procedure was completed in which participants received shocks of increasing intensity until the shock level felt "highly annoying but not painful." The maximum shock level a participant could achieve was 5-mA. The mean shock level across the entire sample was 2.10-mA (SD = 1.22), and there were no main effects for Depression Status, $F(1, 168) = 0.76$, *ns*, Panic Status, $F(1, 168) = 0.08$, *ns*, or a Depression Status X Panic Status interaction, $F(1, 168) = 0.20$, *ns*, suggesting the diagnostic groups were comparable on shock level.

The NPU-startle task was modeled after that used by Grillon and colleagues (Schmitz & Grillon, 2012) and included three within-subjects conditions - no shock (N), predictable shock (P), and unpredictable shock (U). Text at the bottom of the computer monitor informed participants of the current threat condition by displaying the following information: "no shock" (N), "shock possible during square" (P), or "shock possible at any time" (U). Each condition lasted 90-s, during which an 8-s geometric cue (blue circle for N, red square for P, green star for U) was presented four times. Interstimulus intervals (ISIs) ranged from 7-15-s (M = 11.6-s), during which only the text describing the condition was on the screen. In the N condition, no shocks were delivered. In the P condition, participants could only receive a shock when the cue (red square) was on the screen. In the U condition, shocks were administered at any time (i.e., during the cue or ISI). Startle probes were presented both during the cue (2-7-s following cue onset) and ISI (4-12-s following ISI onset). No more than one startle probe was delivered during each presentation of the cue or ISI.

The experiment consisted of two recording blocks, with a 5-minute rest period between blocks. Blocks consisted of two presentations of the three conditions in the following orders (counterbalanced): PNUNPU or UPNUNP. The cue appeared four times during each 90-s condition. In between the blocks, participants reported on their emotional state during the task (see below). All participants received 12 shocks (6 during P and 6 during U) and 72 startle probes (24 during each of N, P, and U). The time interval between a shock and a

subsequent startle probe was always greater than 10-s to ensure that startle responses were not affected by an immediately preceding shock.

All stimuli for the task were administered using PSYLAB (Contact Precision Instruments, London, UK) and psychophysiological data were acquired using Neuroscan 4.4 (Compumedics, Charlotte, NC). Acoustic startle probes were 40-ms duration, 103-dB bursts of white noise with near-instantaneous rise time presented binaurally through headphones. Electric shocks lasted 400-ms and were administered to each participant's left wrist.

Startle response was recorded from two 4-mm Ag/AgCl electrodes placed over the orbicularis oculi muscle below the right eye and the ground electrode was at the frontal pole (AFZ). As per published guidelines (Blumenthal et al., 2005), one electrode was 1-cm below the pupil and the other was 1-cm lateral of that electrode. Data were collected using a bandpass filter of DC-200 Hz at a sampling rate of 1,000 Hz.

Slot EEG Task and Physiological Recordings—A computerized slot machine paradigm previously used by Shankman et al. (2007) was used to assess reward sensitivity. The task consisted of three reels of numbers and fruit, which spun simultaneously for 11-s and then landed on a result. To start the reels spinning, participants pressed a button with both thumbs that pulled a lever on the computer screen. The task included 60 spins that were divided into two possible outcomes of 30 trials each – a reward condition (R) in which participants won money if the reels landed on three fruits and a no incentive condition (NI) in which participants were ineligible to win money no matter the outcome. Thus, the R condition was designed to elicit reward anticipation while the NI condition served as a control for several aspects of the R condition (e.g., visual input, anticipating an outcome). The amount of money that could be won during each R trial ranged from $0.50–$3.00.

Trials were presented in a pseudo-random order and there were never more than two consecutive trials of similar type or outcome. Participants began the game with $2.00 and were told the specific condition (R or NI) prior to each trial, but not the potential dollar amount in each R condition. Unbeknownst to the participant, half of the trials in each condition landed on three fruits. Trials were divided into three blocks. Participants completed retrospective ratings of their emotional state for each condition after the first and second blocks (see below). At the end of the task, all participants were given their winnings ($12.00) in cash.

EEG data were recorded from Ag/AgCl electrodes in a 64-channel stretch-lycra electrode cap. The ground electrode was at the frontal pole (AFZ) and the online reference was between CZ and CPZ. VEOG and HEOG electrodes monitored vertical and horizontal eye movements, respectively. Electrode impedances were under 5,000 ohms, and homologous sites (e.g., F3/F4) were within 1,500 ohms of each other. Data were recorded through a Neuroscan Synamp2 data acquisition system at a gain of 10K (5K for eye channels) with a bandpass of DC-200 Hz. Data were acquired at an A/D rate of 1,000 Hz. EEG data were re-referenced offline to the average data from left and right mastoids (i.e., "linked" mastoids).

Verbal Ratings—After each block of the NPU-startle task, participants rated their level of nervousness/anxiety during the cues and ISIs for each condition (i.e., N_{ISI}, N_{Cue}, P_{ISI}, P_{Cue}, U_{ISI}, U_{Cue}) on a scale from 1='Not at all' to 7='Extremely'. Similarly, at the end of the first two blocks of the slot EEG task, participants rated how much they looked forward to three fruits during both the R and NI conditions on a scale from 1='Not at all' to 7='Extremely'. Separate analysis of the block 1 and block 2 emotion ratings yielded nearly identical results, so the present study used the average rating of the two administrations.

Physiological Data Processing—Details regarding physiological data processing are provided in Shankman et al. (2013). Briefly, startle blinks were scored according to guidelines provided by Blumenthal et al. (2005). Analyses were conducted using blink magnitude (i.e., condition averages included values of 0 for non-response trials), as this is a more conservative estimate of blink response (Blumenthal et al., 2005). Blink magnitudes were also standardized within-subjects using T-scores, which reduces the influence of outlier blink responses. Seven participants (3 MDD only, 3 comorbids, and 1 control) were excluded from analyses because they produced fewer than 2 scoreable blinks in any single condition and one participant (MDD only) was excluded because of equipment failure, leaving a final sample of 165 (28 MDD only, 26 PD only, 51 comorbids, and 60 controls). Diagnostic groups did not differ in the number of missing blinks (all p's > .49).

EEG data from the 11-s spinning interval was segmented into consecutive 1.024-s epochs every 0.512 s (50% overlap). Power spectra were computed offline from EEG data by using a fast Fourier transform. The average absolute alpha power was computed for each electrode site and then natural log transformed in order to normalize the data. For consistency with previous research (Bruder et al., 2005), the alpha band was defined as 7.81–12.70 Hz and used as an inverse measure of regional brain activity. Asymmetry scores were computed for the R and NI conditions by subtracting power at left electrodes from power at homologous right electrodes (e.g., F8-F7), so that the higher values reflected greater activity in left relative to right regions. Frontal EEG asymmetries between homologous electrode pairs (F3/4, F5/6, F7/8) were averaged together to create a composite frontal EEG asymmetry score. Similarly, parietal EEG asymmetries between homologous electrode pairs (P3/4, P5/6, P7/8) were averaged together to create a composite parietal EEG asymmetry score. The composite EEG asymmetry scores were calculated because Shankman et al. (2013) found similar diagnostic group differences for all three recording sites in both frontal and parietal regions. Parietal EEG asymmetry was included to test for topographical specificity of any effects, as depression and anxiety have been associated with abnormal EEG asymmetry over parietal sites (e.g., Bruder et al., 2005).

The sample of participants for the EEG analyses was taken from the 165 participants with good startle data. Nine participants (1 MDD only, 2 PD only, 3 comorbids, and 3 controls) were excluded from EEG analyses due to excessive artifacts in electrodes of interest in the NI or R condition, leaving a final sample of 156 (27 MDD only, 24 PD only, 48 comorbids, and 57 controls).

Data Analysis

Proband group differences in sex, ethnicity, alcohol use disorder, drug use disorder, and current psychiatric medication use were examined using χ^2 tests. Group differences in proband age, education, GAF, HAM-D, and BAI were examined using a 2(Depression Status: Present vs. Absent) X 2(Panic Status: Present vs. Absent) repeated measures analysis of variance (ANOVA).

Both the NPU-startle task and slot EEG task contained control conditions (N and NI conditions, respectively) from which change scores were calculated. Thus, for the NPU-startle task, responses during the N condition were subtracted from responses during the P and U threat conditions (i.e., P-N, U-N). Similarly, for the slot EEG task, responses during the NI condition were subtracted from responses during the R condition (i.e., R-NI). For both sets of analyses, if the change scores were significantly associated with family history of psychopathology, follow-up analyses examined whether the induction condition or control condition was driving the effect. Startle potentiation during the U_{ISI} and U_{Cue} were averaged together (i.e., $U_{ISI+Cue}$) given that (1) both periods were identical in meaning as

participants could receive shocks during both the ISI and cue, and (2) startle responding during the ISI and cue of the U condition did not differ (p = .94; see Shankman et al., 2013).

As previously mentioned, family history was dichotomized as Absent vs. Present. Family history was not defined continuously (e.g., density scores), because (1) only two families had more than one relative with PD, (2) a continuous variable would not take into account the fact that probands may not be equally familiar with each family member's psychiatric history, and (3) Milne et al. (2008) reported comparable strengths of associations between proband and familial psychopathology across multiple definitions of family history scores.

To examine whether sensitivity to threat and sensitivity to reward were associated with family history of psychopathology, psychophysiology and verbal measures were z-transformed, which allowed for direct comparison of odds ratios of independent variables. Next, separate logistic regression analyses were conducted on family history of PD (Present vs. Absent), depression (Present vs. Absent), and alcohol use disorder (Present vs. Absent).

To examine whether sensitivity to threat and sensitivity to reward were associated with family history of psychopathology independent of current DSM-IV diagnosis, the above models were run using hierarchical logistic regression with additional independent variables for proband diagnoses (Depression Status and/or Panic Status [also z-transformed]) that were associated with each family history variable.

Means and standard deviations for psychophysiological and verbal measures across the entire sample are presented in parentheses.

Results

Demographics and Clinical Characteristics

Participant demographics and clinical characteristics are presented in Table 1. Groups did not differ on age, sex, education, or ethnicity (all p's > .10). MDD participants (MDD only and comorbids) had greater HAM-D scores relative to non-MDD participants (PD only and controls). PD participants (PD only and comorbids) had greater BAI scores relative to controls, but only comorbid participants had greater BAI scores relative to MDD only participants. PD only and MDD only participants did not differ on BAI scores.

Groups differed on rates of lifetime alcohol use disorder, lifetime substance use disorder, and current psychiatric medication use. Therefore, these variables (z-transformed) were included as block 2 covariates in all subsequent analyses involving proband Depression Status and/or Panic Status.

Threat Sensitivity and Family History of PD

Startle—Results indicated that heightened startle to the $U_{ISI+Cue}$ (M = 7.36 T-score difference, SD = 3.61) was associated with a *greater* likelihood of having at least one first-degree relative with a lifetime history of PD. In contrast, startle potentiation to the P_{Cue} (M = 8.34 T-score difference, SD = 4.77) was not associated with family history of PD, suggesting that the effect was specific to unpredictable threat (see Table 2).[2],[3]

[2]The FHS also assesses other anxiety disorders beyond PD. Therefore, the present study examined whether startle potentiation was associated with family history of (1) any anxiety disorder, (2) 'fear' disorders (i.e., PD, agoraphobia, specific phobia, and social phobia), or (3) agoraphobia, specific phobia, or social phobia individually. Results indicated that neither startle potentiation to the P_{Cue} nor $U_{ISI+Cue}$ were associated with family history of any anxiety disorder (p's > .39), 'fear' disorders (p's > .18), or agoraphobia, specific phobia, or social phobia individually (all p's > .35). These results are not surprising given the heterogeneity of anxiety disorders (Watson, 2005), and suggest that, of the anxiety disorders measured by the FHS, heightened sensitivity to unpredictable threat is particularly associated with familial risk for PD.

To follow-up the significant $U_{ISI+Cue}$ change score analysis, we examined whether startle during the $U_{ISI+Cue}$ and $N_{ISI+Cue}$ conditions alone were associated with family history of PD. As expected, results indicated that startle during the $U_{ISI+Cue}$ threat condition (M = 51.82 T-score, SD = 2.79) was associated with family history of PD, OR = 1.70 (95% CI = 1.05–2.75), $p < .05$. Importantly, startle during the $N_{ISI+Cue}$ threat condition (M = 44.46 T-score, SD = 2.37) was not associated with family history of PD, OR = 1.02 (95% CI = 0.69–1.49), *ns*, suggesting that startle during the $U_{ISI+Cue}$ threat condition was driving the effect.

The interaction between proband PD Status and startle to $U_{ISI+Cue}$ threat was not associated with family history of PD (p = .29) when added as a block 5 independent variable, suggesting that unpredictable threat sensitivity was not moderated by proband diagnosis.

Verbal Anxiety—Neither verbal anxiety potentiation during the P_{Cue} (M = 2.73 arbitrary units difference, SD = 1.69), OR= 0.86 (95% CI = 0.58–1.27), *ns*, or the $U_{ISI+Cue}$ (M = 3.04 arbitrary units difference, SD = 1.82), OR = 0.95 (95% CI = 0.64–1.41), *ns*, was associated with family history of PD. The null results were not due to insufficient sensitivity of the verbal anxiety measure to the experimental manipulations because participants reported greater verbal anxiety during P_{Cue} relative to N_{Cue} and $U_{ISI+Cue}$ relative to $N_{ISI+Cue}$ (see Shankman et al. [2013] for these analyses).

Reward Sensitivity and Family History of Depression

EEG—Frontal EEG asymmetry (M = 0.013 α-power difference, SD = 0.061) was associated with family history of depression (see Table 2), such that a *reduced* left frontal EEG asymmetry while anticipating reward was associated with a *greater* likelihood of having at least one first-degree relative with a lifetime history of depression.[3]

To follow-up the significant frontal EEG asymmetry change score analysis, we examined whether frontal EEG asymmetry during the R and NI conditions alone were associated with family history of depression. Results indicated that neither frontal EEG asymmetry during the R condition (M = 0.026 α-power, SD = 0.18, OR = 1.16 [95% CI = 0.83–1.61], *ns*) nor EEG during the NI condition (M = 0.013 α-power, SD=0.18, OR = 5.91 [95% CI = 0.85–41.35], *ns*) was associated with family history of depression. Thus, these results suggest that it was the relative difference between the R and NI conditions that was associated with family history of depression.

The interaction between proband Depression Status and frontal EEG asymmetry was not associated with family history of depression when added as a block 5 independent variable (p = .20), suggesting that reward sensitivity was not moderated by proband diagnosis.

Logistic regression analyses indicated that parietal EEG asymmetry (M = −2.68 α-power difference, SD = 6.15) was not associated with family history of depression, OR = 1.03 (95% CI = 0.98–1.09), *ns*, suggesting that the association between EEG asymmetry and family history of depression was specific to the frontal region.

Verbal Excitement—Verbal excitement (M = 2.68 arbitrary units difference, SD = 1.88) was not associated with family history of depression, OR = 1.03 (95% CI = 0.86–1.24), *ns*. Similar to verbal anxiety, the null results were not due to insufficient sensitivity of the verbal excitement measure to the experimental manipulation because participants reported

[3] $U_{ISI+Cue}$ startle potentiation was still associated with family history of PD at a trend level after including BAI as a covariate, OR = 1.54 (95% CI = 0.94–2.51), $p < .09$. Frontal EEG asymmetry remained significantly associated with family history of depression after including HAM-D scores as a covariate, OR = 0.67 (95% CI = 0.46–0.98), $p < .05$.

greater verbal excitement during R relative to NI condition (see Shankman et al. [2013] for these analyses).

Specificity of Associations

To assess the discriminant validity of sensitivity to threat and sensitivity to reward, the present study examined whether they were associated with family history of depression and anxiety, respectively (see Table 2). Results indicated that startle potentiation during the P_{Cue} and $U_{ISI+Cue}$ were *not* associated with family history of depression. Similarly, frontal EEG asymmetry was *not* associated with family history of PD.

To further assess discriminant validity, the present study examined whether sensitivity to threat and sensitivity to reward were associated with family history of alcohol use disorder (see Table 2). Results indicated that *reduced* startle potentiation to $U_{ISI+Cue}$ was associated with a *greater* likelihood of having a family history of an alcohol use disorder. All other psychophysiology or verbal measures were not associated with family history of alcohol use disorders.

Controlling for Proband DSM-IV Diagnosis

Finally, the present study examined whether sensitivity to unpredictable threat and reward were associated with family history of psychopathology independent of proband DSM-IV diagnosis. A model with family history of PD as the dependent variable and proband Depression Status (Present vs. Absent), Panic Status (Present vs. Absent), and the interaction as independent variables (all z-transformed) yielded a significant main effect for Panic Status, OR = 1.92 (95% CI = 1.22–3.01), $p < .01$, and a Depression Status by Panic Status interaction, OR = 0.63 (95% CI = 0.41–0.98), $p < .05$, but no main effect for Depression Status (OR = 1.48). A similar model for family history of depression yielded a significant main effect for Depression Status OR = 1.98 (95% CI = 1.39–2.80), $p < .001$, but not Panic Status (OR = 1.14) nor the interaction (OR = 0.87). The model for family history of alcohol use disorder yielded a significant main effect for Depression Status OR = 2.32 (95% CI = 1.16 – 4.63), $p < .005$, but not Panic Status (OR = 1.70) nor the interaction (OR = 0.51) (see bottom of Table 1 for percentages).[4] Thus, for the family history of PD-startle model, proband Panic Status, Depression Status, and Panic Status X Depression Status were included as independent variables in block 3. For the family history of depression-EEG asymmetry and family history of alcohol use disorder-startle models, proband Depression Status was included as an independent variable in block 3. For all analyses, the psychophysiology variable was entered in block 4.

Results indicated that the psychophysiological measures were still associated with family history of psychopathology even after controlling for proband diagnosis (see Table 3). More specifically, startle potentiation to $U_{ISI+Cue}$ threat continued to be associated with family history of PD and alcohol use disorder independent of proband DSM-IV diagnosis. Frontal EEG asymmetry also continued to be associated with family history of depression independent of proband DSM-IV diagnosis.

[4]In probands with a positive family history of PD, 51.5% identified their mother, 15.2% identified their father, 27.3% identified their sibling, and 9.1% identified their child. In participants with a positive family history of MDD, 50.9% identified their mother, 29.8% identified their father, 50.9% identified their sibling, and 14.0% identified their child. These percentages did not differ as a function of proband sex or diagnosis (all p's > .10). If probands who only had a disorder in their children (and not their parent/sibling) were excluded, the pattern of results remained.

Discussion

The present study examined whether biomarkers for two proposed mechanisms of dysfunction in anxiety and depression (increased sensitivity to threat and decreased sensitivity to reward, respectively) were associated with an indicator of risk for psychopathology – family history. Results indicated that heightened startle while anticipating unpredictable (but not predictable) threat was associated with increased familial liability for PD (but not depression). Additionally, reduced left frontal EEG asymmetry while anticipating reward relative to no incentive was associated with an increased familial liability for depression (but not PD). Finally, and most interestingly, both of these associations remained significant after controlling for proband DSM-IV diagnosis. Overall, results from the present study suggest that sensitivity to unpredictable threat and reward provide incremental validity over and above DSM-IV diagnoses of depression and anxiety in their association with risk.

Mechanisms of Dysfunction

The present results have important implications for understanding risk for PD (and perhaps 'fear' disorders more broadly). Grillon et al. (2008) provided two potential explanations for the link between sensitivity to unpredictable threat and PD. In the first explanation, heightened sensitivity to unpredictable threat is acquired (or learned) through repeated experiences with un-cued, 'out of the blue' panic attacks. In turn, this acquired sensitivity contributes to the development and worsening of PD because the associated anticipatory anxiety potentiates subsequent panic symptoms (Bouton, Mineka, & Barlow, 2001). In the second explanation, heightened sensitivity to unpredictable threat is viewed as a trait-like vulnerability factor for PD. That is, those with heightened sensitivity to unpredictable threat may have a lowered threshold toward the development of PD after experiencing panic attacks. As approximately 28.3% of the population experience panic attacks, but only 4.8% go on to develop PD (Kessler et al., 2006), it is possible that only those with this vulnerability progress to the full disorder.

Results from the present study are more consistent with the vulnerability explanation. Across all participants heightened startle potentiation to unpredictable threat was associated with increased familial liability for PD, even after controlling for proband PD diagnosis. In other words, heightened startle potentiation to unpredictable threat still indexed risk for PD over and above the variance explained by proband PD diagnosis (and anxiety diagnoses overall, see Pine et al., 2005 for a similar conclusion).

It is important to highlight that the present results cannot definitively rule out the 'acquired' or 'learned' explanation. It is possible that probands may have witnessed a family member's anxiety and received messages from the relative that unexpected bodily sensations are dangerous or harmful. More research is therefore needed to determine what causes the development of heightened sensitivity to unpredictable threat and how it transitions from risk to PD.

PD is characterized by periods of intense fear (i.e., panic attacks) and anticipatory anxiety (e.g., concerns about future panic attacks). As laboratory studies have suggested that fear is elicited by predictable threat and anxiety by unpredictable threat, it is possible that PD would be associated with hypersensitivity to both types of threat. Indeed, Shankman et al. (2013) reported this finding using data from the present sample, although Grillon et al. (2008) found that PD was *only* associated with response to unpredictable threat. Interestingly, results from the present study indicated that only response to unpredictable threat was associated with familial liability for PD. One potential interpretation of this finding is that hypersensitivity to unpredictable threat indexes risk for PD, whereas

hypersensitivity to predictable threat may be an epiphenomenon of the disorder not associated with risk. In other words, heightened sensitivity to unpredictable threat may be found in those who are at risk or currently experiencing PD, while heightened sensitivity to predictable threat may only be evident in those currently experiencing the disorder (and given the lack of replication across studies, may only be an association found in certain contexts).

Reduced sensitivity to reward has long been considered to be one of the fundamental deficits of depression (Meehl, 1975), and numerous studies have tested the hypothesis that this deficit is associated with an abnormal frontal EEG asymmetry (Davidson et al., 2002; Thibodeau et al, 2006). As previously mentioned, one limitation of this research has been the reliance on measuring frontal EEG asymmetry while at rest and not during an approach-related context (Coan et al., 2006). The present study therefore measured EEG asymmetry during a task designed to elicit approach motivation (Shankman et al., 2007) and also examined whether the biomarker was associated with risk for depression. Across all participants, frontal EEG asymmetry while anticipating reward was associated with increased familial liability for depression, even after controlling for proband MDD diagnosis. In other words, frontal EEG asymmetry still indexed risk for depression over and above the variance explained by proband MDD diagnosis. Therefore, results from the present study suggest that reduced sensitivity to reward may index vulnerability for depression.

Diagnostic Categories and the Research Domain Criteria (RDoC) Initiative

The National Institute of Mental Health (NIMH) recently put forth the RDoC initiative, which seeks to identify transdiagnostic dimensions that reflect core mechanisms of psychopathology (Cuthbert & Insel, 2010; Sanislow et al., 2010). RDoC is an exciting direction for the field as it may eventually yield a new nosology for mental illness that moves beyond the problematic DSM categories, and identifies core mechanisms that, at least partially, play an etiological role in psychopathology. In recent RDoC workshops, the constructs examined in the present study - responses to acute threat (fear), potential harm (anxiety), and approach motivation - were identified as potential domains of interest (NIMH, 2011a, 2011b). Results from the present study provide preliminary evidence that the RDoC domains ‘potential harm’ and ‘approach motivation’ are associated with risk. The present study also demonstrated discriminant validity for these domains as the former was associated with familial risk for PD (and not depression) and the latter was associated with familial risk for depression (and not PD). These results suggest that it is important for RDoC studies, which are in their infancy, to not only examine whether domains are transdiagnostic, but also to examine whether they are associated with separate psychopathological constructs (Kendell & Jablensky, 2003).

It should be noted that sensitivity to threat and reward may not be unique to internalizing psychopathology as *insensitivity* to threat and *heightened* sensitivity to reward may be key features for certain externalizing psychopathologies (e.g., psychopathy, Patrick, 1994). That is, the dimensions may be bipolar where either end is problematic. Indeed, the present study found that heightened sensitivity to unpredictable threat was associated with risk for PD, but *reduced* sensitivity to unpredictable threat was associated with risk for alcohol use disorder. This result supports previous findings that reduced startle potentiation to unpleasant stimuli is associated with risk for alcoholism (Miranda, Meyerson, Buchanan, & Lovallo, 2002), as well as other externalizing disorders (Patrick, 1994). Although there are likely other RDoC domains beyond sensitivity to unpredictable threat that increase risk for alcohol problems, these results illustrate the importance of examining RDoC domains in both internalizing and externalizing psychopathologies in the same sample.

Clinical Implications

There are several clinical implications from the present study. For decades, researchers have longed for objective, laboratory-based measures to augment diagnostic validity and address the limitations of relying on subjective reporting of symptoms (Hyman, 2007). Finding biomarkers that add incremental diagnostic validity is an important step, and measures such as heightened startle to unpredictable threat and abnormal EEG asymmetry while anticipating reward may be worth considering for PD and depression constructs, respectively – particularly given the relative ease in which these measures could be administered. However, future research is needed to examine the sensitivity and specificity of these measures as well as their ability to prospectively predict important outcomes, such as treatment response.

Limitations

The present study had several limitations. First, family history of psychopathology was determined by interviewing probands about the psychopathology in their relatives, an approach that has been shown to have good specificity but low sensitivity (Andreasen et al., 1977). Therefore, the present study may have underestimated the prevalence of psychopathology in probands' relatives. Second, family history and proband diagnostic interviews were conducted by the same interviewer, and this may have artificially inflated the relationship between proband and familial psychopathology. However, this is unlikely given that the family history measure was a fully-structured interview that did not require subjective interpretation by the interviewer. Third, depressed participants were limited to those with early-onset depression, and results from the present study may not generalize to all types of depression (e.g., adult-onset depression). Fourth, only the EEG asymmetry change score between the R and NI conditions was associated with family history of depression. Thus, it is difficult to decipher whether the frontal EEG asymmetry effects were driven by blunted activation to R or elevated activation to NI. Fifth, the size of the PD only ($n = 26$) and MDD only ($n = 28$) groups were small, and this may have limited the ability to detect Panic Status by Depression Status interactions. Finally, the psychophysiological variables explained only a modest amount of the variance in risk for psychopathology (~4%), and the diagnostic utility of these biomarkers remains unclear.

Conclusion

In summary, the present study found that heightened sensitivity to unpredictable threat and reduced sensitivity to reward were uniquely associated with familial risk for PD and depression, respectively. In addition, both measures remained associated with familial risk even after adjusting for proband DSM-IV diagnosis, suggesting that each measure added incremental validity. However, it is important to highlight that the psychophysiological variables explained only a modest amount of the variance in risk for psychopathology and further research is needed to more comprehensively understand their diagnostic utility. Overall, these results provide preliminary evidence that adding objective psychophysiological biomarkers of these emotional/motivational dimensions may improve diagnostic validity for PD and depression.

Acknowledgments

This work is based on a dissertation submitted to the University of Illinois-Chicago (UIC) by B.D.N. This study was supported by NIMH Grant R21MH080689 (awarded to S.A.S.) and the NIH Center for Advancing Translational Sciences, UL1TR000050 (awarded to UIC).

References

Andreasen NC, Endicott J, Spitzer RL, Winokur G. The family history method using diagnostic criteria: Reliability and validity. Archives of General Psychiatry. 1977; 34:1229–1235. [PubMed: 911222]

Beck A, Epstein N, Brown G, Steer R. An inventory for measuring clinical anxiety - psychometric properties. Journal of Consulting and Clinical Psychology. 1988; 56:893–897.10.1037/0022-006X.56.6.893 [PubMed: 3204199]

Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clinical Pharmacology & Therapeutics. 2001; 69:89–95.10.1067/mcp.2001.113989 [PubMed: 11240971]

Blumenthal TD, Cuthbert BN, Filion DL, Hackley S, Lipp OV, van Boxtel A. Committee report: Guidelines for human startle eyeblink electromyographic studies. Psychophysiology. 2005; 42:1–15.10.1111/j.1469-8986.2005.00271.x [PubMed: 15720576]

Bouton ME, Mineka S, Barlow DH. A modern learning theory perspective on the etiology of panic disorder. Psychological Review. 2001; 108:4–32.10.1037/0033-295X.108.1.4 [PubMed: 11212632]

Bruder GE, Tenke CE, Warner V, Nomura Y, Grillon C, Hille J, Weissman MM. Electroencephalographic measures of regional hemispheric activity in offspring at risk for depressive disorders. Biological Psychiatry. 2005; 57:328–335.10.1016/j.biopsych.2004.11.015 [PubMed: 15705347]

Clark LA, Watson D, Mineka S. Temperament, personality, and the mood and anxiety disorders. Journal of Abnormal Psychology. 1994; 103:103–116.10.1037/0021-843X.103.1.103 [PubMed: 8040472]

Coan JA, Allen JJB, McKnight PE. A capability model of individual differences in frontal EEG asymmetry. Biological Psychology. 2006; 72:198–207.10.1016/j.biopsycho.2005.10.003 [PubMed: 16316717]

Cuthbert B, Insel T. The data of diagnosis: new approaches to psychiatric classification. Psychiatry. 2010; 73:311–314.10.1521/psyc.2010.73.4.311 [PubMed: 21198381]

Davidson RJ, Pizzagalli D, Nitschke JB, Putnam K. Depression: Perspectives from affective neuroscience. Annual Review of Psychology. 2002; 53:545–574.10.1146/annurev.psych.53.100901.135148

Davis M. Neural systems involved in fear and anxiety measured with fear-potentiated startle. American Psychologist. 2006; 61:741–756.10.1037/0003-066X.61.8.741 [PubMed: 17115806]

First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Clinician Version (SCID-CV). Washington D.C: American Psychiatric Press; 2002.

Gotlib IH, Ranganath C, Rosenfeld JP. Frontal EEG alpha asymmetry, depression, and cognitive functioning. Cognition & Emotion. 1998; 12:449–478.10.1080/026999398379673

Grillon C, Baas JMP, Pine DS, Lissek S, Lawley M, Ellis V, Levine J. The benzodiazepine alprazolam dissociates contextual fear from cued fear in humans as assessed by fear-potentiated startle. Biological Psychiatry. 2006; 60:760–766.10.1016/j.biopsych.2005.11.027 [PubMed: 16631127]

Grillon C, Lissek S, Rabin S, McDowell D, Dvir S, Pine DS. Increased anxiety during anticipation of unpredictable but not predictable aversive stimuli as a psychophysiologic marker of panic disorder. American Journal of Psychiatry. 2008; 165:898–904.10.1176/appi.ajp.2007.07101581 [PubMed: 18347001]

Hamilton M. A rating scale for depression. Journal of Neurology, Neurosurgery & Psychiatry. 1960; 23:56–61.10.1136/jnnp.23.1.56

Hettema JM, Neale MC, Kendler KS. A review and meta-analysis of the genetic epidemiology of anxiety disorders. American Journal of Psychiatry. 2001; 158:1568–1578.10.1176/appi.ajp.158.10.1568 [PubMed: 11578982]

Hyman SE. Can neuroscience be integrated into the DSM-V? Nature Reviews Neuroscience. 2007; 8:725–732.10.1038/nrn2218

Kendell R, Jablensky A. Distinguishing between the validity and utility of psychiatric diagnoses. American Journal of Psychiatry. 2003; 160:4–12.10.1176/appi.ajp.160.1.4 [PubMed: 12505793]

Kendler KS, Prescott CA, Myers J, Neale MC. The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. Archives of General Psychiatry. 2003; 60:929–937.10.1001/archgenpsychiatry.2012.124 [PubMed: 12963675]

Kessler RC, Chiu WT, Jin R, Ruscio AM, Shear K, Walters EE. The epidemiology of panic attacks, panic disorder, and agoraphobia in the national comorbidity survey replication. Archives of General Psychiatry. 2006; 63:415–424.10.1001/archpsyc.63.4.415 [PubMed: 16585471]

Klein DN. Classification of depressive disorders in the DSM-V: Proposal for a two-dimension system. Journal of Abnormal Psychology. 2008; 117:552–560.10.1037/0021-843X.117.3.552 [PubMed: 18729608]

Klein DN, Lewinsohn PM, Seeley JR, Rohde P. A family study of major depressive disorder in a community sample of adolescents. Archives of General Psychiatry. 2001; 58:13–20.10.1001/archpsyc.58.1.13 [PubMed: 11146753]

Krueger RF. The structure of common mental disorders. Archives of General Psychiatry. 1999; 56:921–926.10.1001/archpsyc.56.10.921 [PubMed: 10530634]

Meehl PE. Hedonic capacity: Some conjectures. Bulletin of the Menninger Clinic. 1975; 39:295–307. [PubMed: 1156704]

Melzig CA, Weike AI, Zimmermann J, Hamm AO. Startle reflex modulation and autonomic responding during anxious apprehension in panic disorder patients. Psychophysiology. 2007; 44:846–854.10.1111/j.1469-8986.2007.00560.x [PubMed: 17640268]

Milne BJ, Moffitt TE, Crump R, Poulton R, Rutter M, Sears MR, Caspi A. How should we construct psychiatric family history scores? A comparison of alternative approaches from the Dunedin Family Health History Study. Psychological Medicine. 2008; 38:1793–1802.10.1017/S0033291708003115 [PubMed: 18366822]

Miranda R, Meyerson LA, Buchanan TW, Lovallo WR. Altered emotion-modulated startle in young adults with a family history of alcoholism. Alcoholism: Clinical and Experimental Research. 2002; 26:441–448.10.1111/j.1530-0277.2002.tb02559.x

National Institute of Mental Health. Positive Valence Systems: Workshop Proceedings. 2011a. Retrieved from http://www.nimh.nih.gov/research-funding/rdoc/positive-valence-systems-workshop-proceedings.shtml

National Institute of Mental Health. Negative Valence Systems: Workshop Proceedings. 2011b. Retrieved from http://www.nimh.nih.gov/research-funding/rdoc/negative-valence-systems-workshop-proceedings.shtml

Oldfield RC. The assessment and analysis of handedness: The Edinburgh inventory. Neuropsychologia. 1971; 9:97–113.10.1016/0028-3932(71)90067-4 [PubMed: 5146491]

Patrick CJ. Emotion and psychopathy: Starting new insights. Psychophysiology. 1994; 31:319–330.10.1111/j.1469-8986.1994.tb02440.x [PubMed: 10690912]

Pine DS, Klein RG, Roberson-Nay R, Mannuzza S, Moulton JL III, Woldehawariat G, Guardino M. Response to 5% carbon dioxide in children and adolescents: Relationship to panic disorder in parents and anxiety disorders in subjects. Archives of General Psychiatry. 2005; 62:73–80.10.1001/archpsyc.62.1.73 [PubMed: 15630075]

Robins E, Guze SB. Establishment of diagnostic validity in psychiatric illness: Its application to schizophrenia. American Journal of Psychiatry. 1970; 126:983–986. [PubMed: 5409569]

Sanislow CA, Pine DS, Quinn KJ, Kozak MJ, Garvey MA, Heinssen RK, Cuthbert BN. Developing constructs for psychopathology research: Research domain criteria. Journal of Abnormal Psychology. 2010; 119:631–639.10.1037/a0020909 [PubMed: 20939653]

Schmidt HD, Shelton RC, Duman RS. Functional biomarkers of depression: Diagnosis, treatment, and pathophysiology. Neuropsychopharmacology. 2011; 36:2375–2394.10.1038/npp.2011.151 [PubMed: 21814182]

Schmitz A, Grillon C. Assessing fear and anxiety in humans using the threat of predictable and unpredictable aversive events (the NPU-threat test). Nature Protocols. 2012; 7:527–532.10.1038/nprot.2012.001

Shankman SA, Klein DN. The relation between depression and anxiety: An evaluation of the tripartite, approach-withdrawal and valence-arousal models. Clinical Psychology Review. 2003; 23:605–637.10.1016/S0272-7358(03)00038-2 [PubMed: 12788112]

Shankman SA, Klein DN, Tenke CE, Bruder GE. Reward sensitivity in depression: A biobehavioral study. Journal of Abnormal Psychology. 2007; 116:95–104.10.1037/0021-843X.116.1.95 [PubMed: 17324020]

Shankman SA, Nelson BD, Robison-Andrews EJ, Sarapas C, Campbell ML, Altman SE, Gorka SM. A psychophysiological investigation of threat and reward sensitivity in individuals with panic disorder and/or depression. Journal of Abnormal Psychology. 2013; 122:322–338.10.1037/a0030747 [PubMed: 23148783]

Stewart JL, Bismark AW, Towers DN, Coan JA, Allen JJ. Resting frontal EEG asymmetry as an endophenotype for depression risk: Sex-specific patterns of frontal brain asymmetry. Journal of Abnormal Psychology. 2010; 119:502–512.10.1037/a0019196 [PubMed: 20677839]

Stewart JL, Coan JA, Towers DN, Allen JJB. Frontal EEG asymmetry during emotional challenge differentiates individuals with and without lifetime major depressive disorder. Journal of Affective Disorders. 2011; 129:167–174.10.1016/j.jad.2010.08.029 [PubMed: 20870293]

Thibodeau R, Jorgensen RS, Kim S. Depression, anxiety, and resting frontal EEG asymmetry: A meta-analytic review. Journal of Abnormal Psychology. 2006; 115:715–729.10.1037/0021-843X.115.4.715 [PubMed: 17100529]

Tomarken AJ, Dichter GS, Garber J, Simien C. Resting frontal brain activity: Linkages to maternal depression and socio-economic status among adolescents. Biological Psychology. 2004; 67:77–102.10.1016/j.biopsycho.2004.03.011 [PubMed: 15130526]

Watson D. Rethinking the mood and anxiety disorders: A quantitative hierarchical model for *DSM-V*. Journal of Abnormal Psychology. 2005; 114:522–536.10.1037/0021-843X.114.4.522 [PubMed: 16351375]

Weissman MM, Wickramaratne P, Adams P, Wolk S, Verdeli H, Olfson M. Brief screening for family psychiatric history: The family history screen. Archives of General Psychiatry. 2000; 57:675–682.10.1001/archpsyc.57.7.675 [PubMed: 10891038]

Table 1

Participant Demographics, Clinical Characteristics, and Family History of Psychopathology

	Control (*n*=60)	MDD only (*n*=28)	PD only (*n*=26)	Comorbids (*n*=51)
Demographic variables				
Age (SD)	32.0(13.6)	29.1(12.2)	33.7(13.3)	35.4(10.8)
Sex (% female)	60.0%	71.4%	61.5%	66.7%
Race (% Caucasian)	50.0%	46.4%	42.3%	51.0%
Education (SD)	15.5(2.3)	14.3(1.7)	15.2(2.2)	14.6(2.5)
Clinical variables				
Global Assessment of Functioning (SD)	$89.0(7.4)_a$	$53.6(8.5)_b$	$58.5(9.0)_c$	$51.8(6.4)_b$
Hamilton Depression Scale (SD)	$1.5(1.8)_a$	$24.9(8.8)_b$	$8.6(7.5)_c$	$26.4(8.7)_b$
Beck Anxiety Inventory (SD)	$1.7(2.1)_a$	$12.6(8.5)_b$	$15.8(12.2)_{b,c}$	$20.2(13.7)_c$
Age of onset of first depressive disorder (SD)	-	13.6(2.9)	-	13.4(4.2)
Age of onset of first anxiety disorder (SD)	-	-	$20.9(9.0)_a$	$17.0(9.0)_b$
Alcohol use disorder	$5.0\%_a$	$35.7\%_b$	$30.8\%_b$	$49.0\%_b$
Drug use disorder	$0.0\%_a$	$28.6\%_{b,c}$	$19.2\%_c$	$41.2\%_b$
Currently taking psychiatric medication	$1.7\%_a$	$25.0\%_{b,c}$	$23.1\%_c$	$47.1\%_b$
Family history of psychopathology				
% probands with ≥1 FDR with depression	$16.7\%_a$	$53.6\%_b$	$26.9\%_a$	$51.0\%_b$
% probands with ≥1 FDR with PD	$5.0\%_a$	$25.0\%_b$	$30.8\%_b$	$29.4\%_b$
% probands with ≥1 FDR with alcohol use disorder	$19.7\%_a$	$43.8\%_b$	$38.5\%_b$	$48.1\%_b$

Note. Means or percentages with different subscripts across rows were significantly different in pairwise comparisons ($p < .05$, χ^2 test for categorical variables and Tukey's honestly significant difference test for continuous variables). FDR = First-Degree Relative; MDD = Major Depressive Disorder; PD = Panic Disorder.

Table 2

Logistic Regressions with Threat and Reward Sensitivity as Independent Variables and Family History of Psychopathology as Dependent Variables

	Family History of Depression			Family History of PD			Family History of Alcohol Use Disorder		
	R^2	χ^2	β (95% CI)	R^2	χ^2	β (95% CI)	R^2	χ^2	β (95% CI)
Startle to P_{Cue}	<.01	0.60	1.14 (0.82–1.57)	.01	1.41	1.27 (0.85–1.89)	<.01	0.68	0.87 (0.63–1.21)
Startle to $U_{ISI+Cue}$	<.01	0.02	0.98 (0.71–1.35)	.04	4.08 *	1.52 (1.00–2.31) *	.04	4.32 *	0.70 (0.50–0.98) *
Frontal EEG Asymmetry	.05	6.11 *	0.66 (0.47–0.93) *	<.01	0.08	1.06 (0.71–1.57)	.02	2.36	1.32 (0.92–1.87)

Note. R^2 measured using Nagelkerke R^2. CI = Confidence Intervals; EEG = Electroencephalography; ISI = Interstimulus Interval; P = Predictable.

* $p < .05$.

Table 3

Hierarchical Logistic Regressions with Demographics, Diagnoses, and Threat and Reward Sensitivity as Independent Variables and Family History of Psychopathology as Dependent Variables

	Family History of Depression			Family History of PD			Family History of Alcohol Use Disorder		
	ΔR^2	χ^2	β (95% CI)	ΔR^2	χ^2	β (95% CI)	ΔR^2	χ^2	β (95% CI)
Block 1	.04	4.27		.02	1.62		.03	3.50	
Age			1.02 (1.00–1.05)$^{+}$			1.01 (0.98–1.04)			1.02 (0.99–1.05)
Sex			1.42 (0.70–2.88)			1.62 (0.70–3.76)			1.48 (0.74–2.96)
Block 2	.06	7.99*		.13	14.87**		.16	19.99***	
Medication			1.79 (0.80–4.00)			3.43 (1.43–8.25)**			1.49 (0.65–3.43)
Alcohol Use Disorder			1.41 (0.88–2.24)			0.79 (0.44–1.42)			2.20 (1.34–3.59)**
Drug Use Disorder			1.03 (0.65–1.65)			1.72 (0.99–2.98)$^{+}$			0.92 (0.57–1.47)
Block 3	.08	10.42***		.06	7.52^{+}		.02	1.41	
Depression Status			1.91 (1.28–2.85)**			1.32 (0.80–2.18)			1.28 (0.85–1.91)
Panic Status			-			1.64 (1.01–2.65)*			-
Depression X Panic			-			0.62 (0.39–0.98)*			-
Block 4	.04	5.28*		.04	4.47*		.03	4.05*	
Startle to $U_{ISI+Cue}$			-			1.63 (1.02–2.61)*			0.70 (0.49–1.00)*
Frontal EEG Asymmetry			0.65 (0.45–0.96)*			-			-
Total R^2	.22			.25			.24		

Note. R^2 measured using Nagelkerke R^2. CI = Confidence Intervals; EEG = Electroencephalography; ISI = Interstimulus Interval; P = Predictable; PD = Panic Disorder; U = Unpredictable.

$^{+}p < .10$,

$^{*}p < .05$,

$^{**}p < .01$,

$^{***}p < .001$.