Do Individual Differences in Reward and Threat Sensitivity Predict Family History of Psychopathology?

BY

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DISSERTATION
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This dissertation is dedicated to my parents, Doug and Cheri Nelson, without whom it would never have been accomplished.
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<td>ANOVA</td>
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<td>NA</td>
<td>Negative Affectivity</td>
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<td>NIMH</td>
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<td>NPU</td>
<td>No, Predictable, Unpredictable</td>
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<td>Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders</td>
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SUMMARY

The classification and diagnosis of depression and anxiety disorders has evolved greatly since the introduction of DSM-I. Under the current system (DSM-IV), depression and anxiety disorders are viewed as separate categorical entities that are diagnosed via patient self-report using a syndromal approach. However, despite being a largely reliable diagnostic system, there are still many problems with the current approach (e.g., heterogeneity, comorbidity, reliance on overt clinical presentation) that raise questions as to whether the DSM categories constitute a valid way of classifying depression and anxiety disorders. An alternative approach is to identify underlying mechanisms of dysfunction that move beyond categorical syndromes. The present study examined whether heightened sensitivity to threat and reduced sensitivity to reward predicted a well-established indicator of risk – family history. Specifically, 173 individuals diagnosed with panic disorder (PD), major depressive disorder (MDD), both (comorbids), or healthy controls completed two experimental paradigms designed to assess sensitivity to threat (measured via startle response) and sensitivity to reward (measured via frontal EEG asymmetry). Family history of psychopathology was assessed using the Family History Screen. Results indicated that across all participants: 1) startle potentiation to unpredictable threat was associated with family history of PD (but not depression) and 2) frontal EEG asymmetry while anticipating reward was associated with family history of depression (but not PD). In addition, both measures continued to be associated with family history of psychopathology after controlling for current DSM diagnosis. Results from the present study suggest that including an indicator of sensitivity to unpredictable threat and reward may add to the predictive validity of the current anxiety and depression syndromal constructs, respectively.
I. INTRODUCTION

A. Classification and Diagnosis of Mental Disorders

The classification and diagnosis of mental disorders have changed dramatically over the last 60 years. With the American Psychiatric Association’s first publication of the Diagnostic and Statistical Manual of Mental Disorders (DSM) in 1952, mental disorders were given standard nomenclature by the psychiatric community. Through subsequent revisions over the next half-century, the DSM morphed in both scope (from about 100 conditions to almost 300 conditions) and size (from about 150 pages to roughly 900 pages). The current diagnostic system is likely to change again in the upcoming revision (DSM-5), with proposed modifications such as the reorganization of mood and anxiety disorders (Watson, 2005) and more prominent use of dimensional measures (Helzer et al., 2008; Regier, Narrow, Kuhl, and Kupfer, 2009).

Despite several revisions, there are still many problems with the current classification and diagnostic system of mental disorders. Many of these issues are particularly apparent for the diagnoses of depression and anxiety. For example, depression and anxiety disorders are included in separate sections of the manual (suggesting independent disease processes), yet co-occur at extremely high rates (i.e., approximately 37% – 62% of the time for the different anxiety disorders; Kessler, Chiu, Demler, and Walters, 2005). Additionally, several research findings have brought into question whether depression and anxiety disorders have completely unique etiologies (e.g., Grillon et al., 2005; Kendler, Walters, Neale, and Kessler, 1995; Kendler et al., 2011). In sum, there are questions as to whether the currently used approach (syndromes via DSM-defined criteria) provides the best construct validity (i.e., the extent to which a measure assesses the intended construct; Cronbach and Meehl, 1955) toward identifying mental disorders.
One way to understand these issues further is through a brief historical examination of mental health diagnoses in the United States and the DSM.

B. **Historical Examination of Mental Health Diagnoses**

There was a major advancement in psychiatry in the United States around the time of World War II. Psychiatrists became more involved in the selection and assessment of soldiers for the war, and in turn the United States military developed a classification system of psychiatric disorders titled *Medical 203* (Office of the Surgeon General, 2000). Shortly thereafter, the World Health Organization published the sixth edition of the International Statistical Classification of Diseases, which, for the first time, included a section on mental diseases in addition to traditional medical diseases (World Health Organization, 1949).

In 1952, the American Psychiatric Association published the DSM-I as a stand-alone manual for classifying mental disorders. This version and a second edition (published in 1968) were largely influenced by psychodynamic and psychoanalytic theory (the predominant theoretical orientation at the time), and primarily discussed broad underlying conflicts and maladaptive reactions. Under each disorder, symptoms and general criteria were not specified in detail. Psychiatrists at that time argued that diagnosis could be injurious to the patient (Kendler, Muñoz, and Murphy, 2010). While DSM-I and II were major advances for the field of psychiatry, both manuals were shown to have poor reliability (i.e., accuracy and reproducibility) of diagnoses due to criterion variance (i.e., using different diagnostic criteria) and information variance (i.e., relying on different sources of information; Spitzer and Fleiss, 1974).

In 1980, the DSM was revised with the goal of improving the reliability of diagnoses. Of note is that while the hope was that diagnoses would be valid, the primary goal of creating DSM-III was to improve the reliability of diagnoses. Additionally, the DSM was also revised with the
desire to be more scientific and bring psychiatry closer to other disciplines in medicine by establishing standardized diagnostic criteria. Criteria for the disorders were influenced by both the Feighner criteria (Feighner et al., 1972) and the Research Diagnostic Criteria (Spitzer, Endicott, and Robins, 1978). Both of these sets of criteria made several lasting contributions that are part of the system today (Kendler et al., 2010), including the use of operationalized criteria, emphasizing more than the acute clinical picture (e.g., course), relying on empirical data over clinical wisdom, and the idea that criteria are tentative and will change with new data.

The current system for classifying disorders (DSM-IV; APA, 1994) is largely similar to the revised version from 1980. Mental disorders are typically determined via the patient’s subjective report of their symptoms. Patients may be interviewed using a structured interview, such as the Structured Clinical Interview for the DSM (SCID; First, Spitzer, Gibbon, and Williams, 2002), in which an experienced, trained clinician interviews the patient about their psychological problems and determines whether the symptoms of a disorder are present or absent. The interviewer then utilizes diagnostic criteria defined in the DSM-IV to determine the presence or absence of a mental disorder. For example, to meet criteria for major depressive disorder (MDD), the individual must report experiencing depressed mood or diminished interest in almost all activities most of the day, nearly every day, for a period of at least two weeks. In addition, the individual must also report at least 5 of 9 symptoms associated with depression, such as difficulty concentrating, loss of energy, weight loss or gain, etc. This approach has dramatically improved the reliability of psychiatric diagnoses from the earlier versions of the DSM (DSM-II inter-rater reliability coefficients: neurotic depression = .26, psychotic depression = .24, manic-depressive = .33, involutional depression = .30, anxiety reaction = .38; Spitzer and Fleiss, 1974) to the currently used fourth edition (DSM-IV inter-rater reliability coefficients:
major depressive disorder = .66, panic disorder = .67, social phobia = .83, obsessive-compulsive disorder (OCD) = .65, generalized anxiety disorder (GAD) = .75, post-traumatic stress disorder (PTSD) = .77; Lobbestael, Leurgans, and Arntz, 2010).

C. **Validity of Psychiatric Diagnoses**

While the DSM-IV syndromal approach has adequate reliability, there has been increased dissatisfaction with its validity (Kendall and Jablensky, 2003). Validity can be defined as the extent to which a measure assesses what it purports to measure (Raulin and Lilenfeld, 1997). Validity differs from reliability, which is the consistency of a measure (e.g., consistency within itself, over time, method, etc.). However, validity and reliability are related, such that high reliability is necessary for high validity, but not vice versa. There are several different kinds of validity. For example, construct validity refers to the extent to which a given test measures the intended construct (Cronbach and Meehl, 1955). Concurrent validity refers to when a measure is shown to correlate with another measure that has already been validated. Discriminant validity refers to when a measure does not correlate with measures of a distinct, separate construct.

Psychopathology research often involves validation of hypothesized theoretical constructs (e.g., depression) that are not directly observable, but are latent attributes for which indirect evidence is accumulated (cf. Depue et al., 1981).

Robins and Guze (1970) published a seminal article concerning the validity of psychiatric diagnoses. They proposed five phases for developing a valid classification in psychiatry, which included clinical description, laboratory studies, delimitation from other disorders, follow-up studies, and family studies. Concerning family studies, Robins and Guze discuss how the increased prevalence of a disorder among close relatives of the original patient strongly indicates
a valid entity. Therefore, examining whether psychiatric diagnoses aggregate within families provides one way toward assessing the construct validity of a psychiatric disorder.

D. **Family History Methodology**

Familial aggregation of psychiatric diagnoses can be examined using family history methodology. Under this approach, family history is determined by comparing rates of the disorder in biological relatives of affected probands (i.e., index cases) to those in relatives of unaffected probands (i.e., healthy control cases) or probands with a different disorder (i.e., psychiatric control cases). First-degree relatives (i.e., parents, siblings, and offspring) are often given more weight than second-degree relatives given the closer genetic influence (and, on average, environmental influence). This methodology is particularly relevant for research on comorbidity (e.g., depression and anxiety) as it can also help determine reasons/mechanisms of comorbidity, such as whether there is shared familial liability between the conditions or whether they have separate etiologies (Klein and Riso, 1993). Thus, family history studies can argue for or against the separation of psychiatric conditions/constructs. There are two methodological approaches toward assessing family history of psychopathology. In the ‘family study’ method, relatives are directly interviewed to determine psychiatric information. In the ‘family history’ method an informant (typically the proband) is interviewed to determine their family members’ psychiatric information. An advantage of the family study method over the family history method is greater confidence in family member diagnosis. However, the family study method is also more costly, time consuming, and has the potential for selection bias against those who are unavailable for interview (i.e., will not participate or are deceased).

Research has shown that the family history method provides good reliability (Andreasen, Endicott, Spitzer, and Winokur, 1977; Ptok, Seeher, Jessen, Papassotiropoulos, and Heun, 2001;
Rougemont-Buecking et al., 2008; Zimmerman, Coryell, Pföhl, and Stangl, 1988) and specificity of diagnoses (Davies, Sham, Gilvary, Jones, and Murray, 1997; Orvaschel, Thompson, Belanger, Prusoff, and Kidd, 1982; Rougemont-Buecking et al., 2008). However, the family history method has also been shown to have less than adequate sensitivity for depression and anxiety (Andreasen et al., 1977; Orvaschel et al., 1982; Rougemont-Buecking et al., 2008; Weissman et al., 2000) and may underestimate the presence of depression and anxiety in relatives (i.e., false negatives). Indeed, a meta-analysis of the family history method found adequate specificity (depression range: 0.80 - 0.96; anxiety range: 0.89 - 0.99), but relatively low sensitivity for both depression (ranging from 0.19 - 0.71) and anxiety (ranging from 0.05 - 0.52; Hardt and Franke, 2007). Nonetheless, the family history method is a widely used approach toward assessing family history of psychopathology.

E. Does Depression Run in Families?

Using family history methodology, numerous studies have examined whether depression runs in families. Research has indicated that there are elevated rates of depression in family members of depressed probands and this is at a greater rate than in family members of healthy probands (Andreasen, Rice, Endicott, and Coryell, 1987; Gershon et al., 1982; Klein et al., 1995; Klein, Lewinsohn, Seeley, and Rohde, 2001; Shankman, Klein, Lewinsohn, Seeley, and Small, 2008; Weissman et al., 1982). A meta-analysis confirmed that depression runs in families, with family members of depressed probands having an increased risk (odds ratio = 2.84) of depression compared to relatives of control probands (Sullivan, Neale, and Kendler, 2000).

Depression has also been shown to be elevated in family members of probands with premorbid personality characteristics associated with depression (e.g., high neuroticism and rigidity, low extraversion and frustration tolerance) relative to controls (Lauer, Bronisch, Kainz,
and Schreiber, 1997; Maier, Lichtermann, Minges, and Heun, 1992). There are also greater rates of depression in offspring (Biederman et al., 2001; Lizardi, Klein, and Shankman, 2004; Weissman, Leckman, Merikangas, Gammon, and Prusoff, 1984) and grandchildren (Weissman et al., 2005) of depressed probands relative to controls. Finally, there are greater rates of depression in parents of depressed offspring probands compared to controls (Kendler et al., 1997; Weller, Kapadia, Weller, and Fristad, 1994). Overall, there is substantial evidence to suggest the familial aggregation of depression.

There are several characteristics of depression that have been found to impact familial aggregation. For example, several course characteristics, such as an early onset (Sullivan et al., 2000; Weissman et al., 1986; Weissman, 1993), chronic (Klein, Shankman, Lewinsohn, Rohde, and Seeley, 2004), and recurrent course (Gershon, Weissman, Guroff, and Prusoff, 1986; Kendler, Neale, Kessler, Heath, and Eaves, 1994; Kendler, Gardner, and Prescott, 1999; Sullivan et al., 2000; Weissman et al., 1986) have been shown to be associated with more familial depression. In addition, the presence of comorbid anxiety disorder or secondary alcoholism has been shown to increase the risk of depression in relatives (Weissman et al., 1986).

F. **Do Anxiety Disorders Run in Families?**

Similar to depression, anxiety disorders have also been shown to run in families (Kendler et al., 1997; Low, Cui, and Merikangas, 2008b; Merikangas et al., 1998; Shankman et al., 2008). A meta-analysis by Kendler’s group suggested that family members of anxiety disorder probands have an increased risk (odds ratio for panic disorder = 5.0; odds ratio for phobias = 4.1, odds ratio for OCD = 4.0) of anxiety disorders compared to relatives of control probands (Hettema, Neale, and Kendler, 2001).
Given the high rates of comorbidity between depression and anxiety disorders (Kessler et al., 2005), numerous research has also examined whether depression runs in the families of probands with anxiety and thus can test whether there is shared familial liability between the conditions. The results of these studies are mixed with some showing evidence for independent familial liability (Avenevoli, Stolar, Li, Dierker, and Ries Merikangas, 2001; Beiderman, Rosenbaum, Bolduc, and Faraone, 1991; Klein et al., 2001; Klein, Lewinsohn, Rohde, Seeley, and Shankman, 2003; Weissman et al., 1984) and others showing overlap (Kendler et al., 1995; Middeldorp, Cath, Van Dyck, and Boomsma, 2005; Shankman et al., 2008).

However, anxiety disorders are heterogeneous (Mineka, Watson, and Clark, 1998), and familial risk may differ amongst the different anxiety disorders. One way to parse anxiety disorders is ‘fear’ vs. ‘anxious-misery’ disorders (Craske et al., 2009; Krueger, 1999; Vaidnaythan, Patrick, and Cuthbert, 2009; Vollebergh et al., 2001; Watson, 2005). Specifically, ‘fear’ disorders involve intense fear of specific stimuli or situations (e.g., spiders, social interactions, heart palpitations), whereas ‘anxious-misery’ disorders involve the experience of pervasive subjective distress.

Many consider panic disorder (PD) to be the quintessential ‘fear’ disorder, and it has been shown to have one of the highest loadings on the ‘fear’ factor in both twin (Kendler et al., 1995) and factor analytic studies (Vollebergh et al., 2001). In addition, a meta-analysis found the strongest evidence for familial aggregation among the anxiety disorders was for PD (Hettema et al., 2001). Similar to depression, there are characteristics of PD that have been shown to impact familial aggregation. For example, PD with agoraphobia has been shown to be associated with greater familial liability than PD without agoraphobia (Nocon et al., 2008; Noyes et al., 1986).
Similar to anxiety disorders in general, the majority of evidence suggests that PD does not run in the families of probands with depression (Biederman et al., 2001; Goldstein, Weissman, Adams, and Horwath, 1994; Horwath, Wolk, Goldstein, and Wickramaratne, 1995; Low et al., 2008b; Mendlewicz, Papdimitriou, and Wilmotte, 1993; Noyes et al., 1986; Weissman et al., 1983; 1984; although see Maier, Minges, and Licktermann, 1995 for counterevidence). Interestingly, the data are mixed concerning whether depression runs in the families of probands with PD (evidence supporting shared liability: Biederman et al., 1991; Low et al., 2008b; Maier and Lichtermann, 1993; Maier et al., 1995; evidence suggesting independent transmission: Biederman et al., 2001; Crowe, Noyes, Pauls, and Slymen, 1983; Goldstein et al., 1994; Harris, Noyes, Crowe, and Chaudhry, 1983; Noyes, Clancy, Crowe, Hoenk, and Slyman, 1978; Weissman et al., 1993). Therefore, there is some ambiguity as to whether depression and PD are transmitted independently.

In sum, examining the familial aggregation of diagnoses provides one way toward assessing their construct validity. Substantial research has shown that diagnoses of depression and anxiety run in families; however, there is mixed evidence concerning whether depression and anxiety (and PD more specifically) have shared or independent liability. Some of these mixed results may stem from the traditional syndromal approach toward defining depression and anxiety. Thus, there has been increased interest in identifying and defining mental illness based on underlying mechanisms of dysfunction.

G. **Research Domain Criteria**

There are several problems with the currently used subjective, syndromal approach for diagnosing mental disorders. For example, individuals with depression have been shown to have a biased recall and interpretation of events (i.e., depressogenic cognitive style; Alloy et al.,
1999), and this may lead to incorrect reporting of symptoms. In addition, mental disorders can often assume phenomenologically heterogeneous forms, such that two individuals receiving the same diagnosis can present with very different symptom profiles. For example, a 19 year-old male experiencing a depressed mood, difficulty concentrating, psychomotor retardation, insomnia, and weight gain would receive the same diagnosis (MDD) as a 65 year-old female experiencing a diminished interest in most activities, weight loss, psychomotor agitation, feelings of worthlessness and guilt, and suicidal ideation – despite not sharing any symptoms. There is also high comorbidity between disorders (the rate of comorbidity between depression and anxiety disorders ranges from 37% – 62% of the time; Kessler et al., 2005), and symptoms of many disorders overlap with those of other disorders (e.g., depression and PTSD) when they are purported to be categorically distinct syndromes. Finally, and most importantly, the diagnosis of mental illness is based solely on overt clinical presentation and may not capture the fundamental underlying mechanism(s) of dysfunction. The traditional syndromal classification is purely descriptive and does not propose any underlying etiology or core dysfunction. Therefore, while using a subjective, syndromal approach provides a reliable way to diagnose mental disorders, it is unclear whether it identifies a valid disease.

An alternative approach is to define and diagnose psychopathology based on core underlying mechanisms rather than relying on traditional diagnostic categories. This approach has recently been proposed by the National Institute of Mental Health (NIMH), which recently put forth the Research Domain Criteria (RDoC) initiative in response to their strategic goal 1.4 (NIMH, 2011a). RDoC seeks to identify biobehavioral dimensions that are common across several disorders and then relate these dimensions to specific biological processes (Insel et al., 2010; Sanislow et al., 2010). Specifically, RDoC proposes looking at different units of analysis...
(i.e., genes, cells, neural circuits, behaviors) across different domains of interest (i.e., negative affect, positive affect, cognition). Defining groups based on these dimensional domains would help address many of the limitations of the current DSM-based syndromal approach (i.e., comorbidity, heterogeneity, validity).

Two RDoC domains that have been posited to underlie depression and anxiety (as well as other psychopathologies) are sensitivity to reward and threat, respectively (Cuthbert and Insel, 2010; Insel et al., 2009; NIMH, 2011b, c). The next section will provide background for these two constructs and their relation to depression and anxiety. It is important to note, however, that the ‘other ends’ of these dimensions have also been linked to psychopathology. For example, high sensitivity to reward may relate to externalizing disorders and impulse control disorders (e.g., Gatzke-Kopp et al., 2009; O’Brien and Fick, 1996) and low sensitivity to threat may relate to psychopathy/antisocial personality disorder (e.g., Newman, Curtin, Bertsch, and Baskin-Sommers, 2010; Patrick, Bradley, and Lang, 1993). However, as the goal of the present study is to examine the relation between these RDoC dimensions and depression and anxiety, these literatures will not be reviewed.

H. **Heightened Sensitivity to Threat and Anxiety**

Emotional responding to threat can be an evolutionarily advantageous process. In one of the most influential theories on emotion, Lang (1995) describes emotions as ‘action dispositions’ that reflect preparation for action. Therefore, if an organism encounters a threatening predator, such as a snake, the emotional response (i.e., fear) prepares the organism for appropriate action (i.e., run away). However, there are large individual differences in how an organism responds to threat. Individuals with anxiety disorders can be thought of as having a heightened sensitivity to threat. For example, panic disorder (PD) includes a heightened sensitivity to physical symptoms
that are misinterpreted as being dangerous or harmful (Goldstein and Chambless, 1978).

Laboratory studies have repeatedly shown that anxiety disorders, such as PD (Craske and Barlow, 1988), OCD (Steketee, Chambless, Tran, Worden, and Gillis, 1996), and social phobia (Hazen and Stein, 1995), are associated with increased behavioral avoidance of threatening stimuli.

One physiological way to objectively measure sensitivity to threat is through the use of the startle reflex. The startle reflex is a cross-species response to an abrupt, intense stimulus, and is a well-documented indicator of defensive system activation (Lang, 1995; Vrana, Spence, and Lang, 1988). Startle is an evolutionarily primitive response, mediated by a basic neural circuit consisting of the auditory nerve, the ventral cochlear nucleus, the dorsal nucleus of the lateral lemniscus, the caudal pontine reticular nucleus, spinal interneurons, and spinal motor neurons (Davis, Gendelman, Tischler, and Gendelman, 1982; Koch, 1999).

There are several ways to measure the startle response. In humans, the most common way is to present loud, acoustic white noise probes to participants and measure contractions of the obicularis oculi muscle just below the eye (i.e., the muscle that closes the eyelids during a blink; Blumenthal et al., 2005; Lang, Bradley, and Cuthbert, 1990). Startle is a particularly advantageous measurement of threat sensitivity as it provides an online assessment of current emotional states. Specifically, startle has been shown to potentiate (increase) during aversive emotional states, such as fear and anxiety (Lang, Bradley, and Cuthbert, 1998), and attenuate during positive emotional states (Giargiari, Mahaffey, Craighead, and Hutchison, 2005; Lang et al., 1990). Several different aversive stimuli have been shown to reliably potentiate startle, including unpleasant pictures (Lang et al., 1990), unpleasant imagery (Cuthbert et al., 2003),
darkness (Grillon and Ameli, 1998b), airblasts to the throat (Grillon and Ameli, 1998a), and threat of electric shock (Grillon and Ameli, 1998a).

Several studies have shown that anxiety disorders (e.g., PD, PTSD, and social phobia) are associated with heightened baseline startle responding (Grillon, Ameli, Goddard, and Woods, 1994; Larsen, Norton, Walker, and Stein, 2002; Orr, Lasko, Pitman, and Shalev, 1995), however other studies have failed to find differences (Amrhein, Pauli, Dengler, and Wiedemann, 2005; Lissek et al., 2009; Melzig, Weike, Zimmermann, and Hamm, 2007; Miller and Litz, 2004). One explanation for these mixed findings is that a baseline task provides a dispositional assessment of threat sensitivity (Coan, Allen, and McKnight, 2006). Thus, a better approach may be to examine individual differences in threat sensitivity while engaging in an emotional challenge. This is often achieved by manipulating certain features of aversive stimuli.

One feature of aversive stimuli that has been shown to impact responding in anxious individuals is predictability (Grillon et al., 2008; 2009). Several theorists have argued that the predictability of aversive stimuli affects the type of aversive response (Mineka and Kihlstrom, 1978). Animal studies have long shown that, compared to predictable aversive stimuli, unpredictable aversive stimuli yield greater freezing, decreased eating, and physiological changes, such as increased body temperature, increased defecation, and ulceration (Seligman, 1968; Seligman and Maier, 1967; Weiss, 1970). Animal studies have also suggested that aversive responses to predictable and unpredictable threat are mediated by overlapping but separable neuroanatomical systems (Davis, 1998; 2006), specifically the central nucleus of the amygdala for predictable threat, and the bed nucleus of the stria terminalis for uncertain threat (Davis, 2006; Gray and McNaughton, 2000). This distinction has been further supported by Grillon et al.
(2006), who found that benzodiazepine administration attenuated aversive responding in anticipation of unpredictable, but not predictable, threat.

Several researchers have posited that the predictability of aversive stimuli differentiates the emotional response states of fear and anxiety (Barlow, 2000; Grillon et al., 2008; Hamm and Weike, 2005). Fear is important for survival, as it prepares an organism for more immediate fight, flight, or immobilization responses, and is associated with predictable danger. In contrast, anxiety is elicited when the perceived danger is less certain (or present) and requires a sustained state of vigilance and defensive preparedness. The distinction between anxiety and fear is especially relevant for PD, which is characterized by periods of intense fear (i.e., panic attacks) and elevated anxiety (i.e., anxious apprehension in-between panic attacks).

To test the distinction between states of fear and anxiety, Grillon and colleagues (Grillon et al., 2004; Schmitz and Grillon, 2012) developed a startle paradigm called the ‘NPU-threat task’ that manipulates the predictability of aversive stimuli while assessing online aversive state (via response to startle probes; see Figure 1). During the task, participants undergo three different experimental conditions (No threat [N], Predictable threat [P], Unpredictable threat [U]), and during each condition, geometric cues are presented on the screen for 8-s each time. In the N condition, no aversive stimuli were presented. In the P condition, aversive stimuli are presented only when the cue is present on the screen (i.e., the aversive stimuli are predictable). In the U condition, aversive stimuli are presented at any time (i.e., when the cue is on and off the screen), thus the cue does not predict the aversive stimuli. Aversive state is measured by presenting startle probes during the presentation of the cue and in-between cues (i.e., inter-stimulus intervals [ISIs]) of each condition. Several studies and laboratories that have used the NPU-threat task have shown that startle was potentiated during the cue (and not the ISI) of the P condition, and
during the cue and ISI of the U condition, relative to the N condition (Grillon et al., 2004; 2006; Moberg and Curtin, 2009; Nelson and Shankman, 2011; Shankman, Robison-Andrew, Nelson, Altman, and Campbell, 2011). Therefore, whereas predictable threat elicited a cue-specific fear-potentiated startle response, unpredictable threat elicited a more sustained, contextual anxiety response.

Interestingly, Grillon et al. (2008) found that PD was associated with heightened contextual startle response while anticipating unpredictable threat, but normal fear-potentiated startle response while anticipating predictable threat. Thus, Grillon and colleagues concluded that heightened startle responding to unpredictable threat might be a psychophysiological marker for PD. However, Shankman and colleagues (in press) recently found that PD was associated with heightened startle responding while anticipating unpredictable and predictable threat. Nonetheless, heightened responding to unpredictable threat has also been found in other anxiety disorders (e.g., PTSD; Grillon et al., 2009), and thus may represent the common underlying mechanism.

I. Reduced Sensitivity to Reward and Depression

A reduced sensitivity to positive stimuli and reward has been identified as a possible underlying mechanism of depression (Henriques, Glowacki, and Davidson, 1994; Henriques and Davidson, 2000). This hypothesis has been supported by numerous behavioral observations. For example, depressed and dysphoric individuals have been shown to engage in fewer pleasant activities (Lewinsohn and Graf, 1973), exhibit reduced frequency and intensity of facial expressions to pleasant stimuli (Sloan, Strauss, and Wisner, 2001), and reduced spatial attention to positive facial expressions (Suslow, Junghanns, and Arolt, 2001) relative to controls. In addition, individuals with depression have been shown to exhibit a decreased response bias to
reward relative to controls (Henriques and Davidson, 2000; Henriques et al., 1994; Pizzagalli, Jahn, and O’Shea, 2005).

Davidson’s (1992, 1998) approach-withdrawal model attempts to explicate the neurobehavioral origins of reduced sensitivity to reward in depression. The approach-withdrawal model proposes two separate systems of emotion/motivation (Davidson, 1992, 1998; Fowles, 1994; Gray, 1994). The approach system controls appetitive, goal-directed behavior and sensitivity to reward, while the withdrawal system controls behavioral inhibition and avoidance. The approach-withdrawal model suggests that abnormalities in the approach system play an etiological role in the development of depression. Thus, individuals with lower approach motivation tendencies are often characterized as having deficits in reward seeking behavior.

Davidson and colleagues have also proposed that the approach system involves a neural circuit that incorporates the left frontal cortex. This reasoning was based on several lines of research indicating that left frontal regions are important for intention, self-regulation, and planning (Luria, 1973), and maintaining representations of goals and how to achieve them (Davidson, Pizzagalli, Nitschke, and Putnam, 2002). In addition, stroke patients who suffered damage to left frontal regions exhibited behavioral change characterized by deficits in approach-oriented behavior (Gainotti, 1972; Robinson, Kubos, Starr, Rao, and Price, 1983; Robinson, Starr, and Price, 1984; Sackheim et al., 1982). Therefore, the approach-withdrawal theory hypothesizes that left-sided frontal brain regions are particularly involved in approach-related, appetitive goals (Davidson et al., 2002).

While engaging in approach-oriented behavior (such as anticipating a reward), left frontal regions of the brain are more active compared to right frontal regions. This results in an unbalanced, asymmetrical pattern of frontal brain activation (i.e., greater activity in the left
frontal area relative to the right frontal area). As a result, individual differences in sensitivity to reward can be measured by examining the degree of difference between the left and right frontal regions. Since depression has been shown to be associated with a reduced sensitivity to reward, several theorists have hypothesized that depression will be associated with an abnormal frontal brain asymmetry.

Reduced left frontal brain asymmetry in depression has most often been tested through the use of electroencephalography (EEG). EEG measures brain electrical activity using non-invasive recording disks placed on the head, and parameters of interest include the frequency and amplitude of rhythmic waves generated by the thalamus and influenced by the cerebral cortex (Davidson, Jackson, and Larson, 2000). The most commonly examined frequency band is alpha (8-12 Hz), which is believed to be an inverse measure of cortical activity (i.e., cortical activity inhibits the thalamo-cortical alpha rhythm). There is some controversy over the use of alpha as an inverse indicator of brain activity (Allen, Coan, and Nazarian, 2004). However, several studies have shown that alpha measured over various cortical regions is associated with other measures of brain activity, such as functional magnetic resonance imaging (fMRI; Goldman, Stern, Engel, and Cohen, 2002) and positron emission tomography (PET; Oakes, et al., 2004). Additionally, when recorded over particular cortical brain regions, alpha has been shown to be associated with decreased performance on neuropsychological tasks believed to be important to those regions (e.g., Davidson, Chapman, Chapman, Henriques, 1990).

Consistent with expectations, compared to controls several investigations have found reduced relative left frontal EEG asymmetries in currently depressed individuals (Bruder et al., 1997; Henriques and Davidson, 1991), as well as in individuals at risk for (Bruder et al., 2005; Tomarken, Dichter, Garber, and Simien, 2004) and in remission from depression (Gotlib,
Ranganath, and Rosenfeld, 1998; Henriques and Davidson, 1990; Stewart, Bismark, Towers, Coan, and Allen, 2010; although see Reid, Duke, and Allen, 1998). However, most of these investigations examined EEG asymmetry while at rest. Specifically, in resting conditions participants are typically instructed to remain still without any explicit instruction for what to think or how to feel.

There are several issues with using frontal EEG asymmetry while at rest as an indicator of approach motivation/reward sensitivity. For example, research has indicated that approximately 40% of the variance in EEG asymmetry may be due to state effects (Hagemann, Hewig, Seifert, Naumann, and Bartussek, 2005). Coan and colleagues (2006) described the use of a resting condition in examining individual differences in frontal EEG asymmetry as relying on a dispositional model of frontal affective style. The dispositional model theorizes that by minimizing situational demands, underlying emotional and motivational tendencies will manifest. Thus, these underlying tendencies, in combination with environmental demands, determine emotional responding (and in turn risk for psychopathology). In contrast, a capability model encourages measuring frontal EEG asymmetry during a laboratory challenge or induction, and emphasizes examining the degree to which individuals are capable of approach versus withdrawal responses (Mischel, 1973). Coan et al. (2006) examined whether EEG asymmetry is better measured under the dispositional model (i.e., at rest) vs. the capability model (i.e., during an emotional challenge), and found that individual differences in frontal EEG asymmetry were more pronounced during an emotional challenge task compared to a resting task. In addition, EEG asymmetry during the emotional challenge was less prone to measurement error and had a more reliable relationship with criterion measures compared to resting EEG asymmetry.
Therefore, a superior approach to measuring EEG asymmetry may be to measure frontal EEG asymmetry while manipulating approach motivation. To address this issue, Shankman and colleagues (2007) compared frontal EEG asymmetry between depressed and control participants while playing a computerized slot machine game (see Figure 2) designed to elicit approach motivation. Results indicated that adults with childhood or adolescent onset depression exhibited an abnormal frontal EEG asymmetry (reduced left relative to right frontal activation) 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 (i.e., Stewart, Coan, Towers, and Allen, 2011). Overall, the literature suggests that abnormal frontal EEG asymmetry (characterized by a reduced left relative to right asymmetry) may be a potential biobehavioral marker for depression (Coan and Allen, 2004).

J. Present Study

The present study examined whether the two aforementioned mechanisms of dysfunction in depression and anxiety (sensitivity to reward and threat, respectively) were associated with a well-established validator of risk - family history. Specifically, individuals with major depressive disorder (MDD) and/or panic disorder (PD) and healthy controls were interviewed to assess family history of psychopathology using the family history method. Following this, participants completed two experimental tasks designed to assess sensitivity to threat and reward while psychophysiological measurements (startle and EEG) were recorded. There were three primary aims for the present study. First, the present study examined whether sensitivity to reward (as assessed by frontal EEG asymmetry) was associated with family history of depression, and sensitivity to unpredictable/predictable threat (as assessed by startle potentiation) was associated
with family history of PD. Second, the present study examined whether sensitivity to reward/threat was associated with family history of psychopathology independent of proband DSM diagnosis.

Finally, for the third aim the present study examined the specificity of any association between sensitivity to reward and threat and family history of psychopathology. This was important given the high comorbidity between depression and anxiety (Kessler et al., 2005), and the mixed findings regarding shared familial liability between the disorders (Biederman et al., 1991; 2001; Crowe et al., 1983; Maier et al., 1993; 1995; Noyes et al., 1978; Weissman et al., 1993). Relatedly, consistent with the aims of the RDoC initiative, it was important to determine whether the proposed underlying mechanisms of dysfunction were transdiagnostic (and thus predict family history of depression and anxiety disorders) or specific to certain disorders.

The specificity of reward and threat sensitivity may be better understood through theoretical models that have aimed to explain the overlapping and distinct features of depression and anxiety. For example, the tripartite model (Clark and Watson, 1991; Clark, Watson, and Mineka, 1994; see Shankman and Klein, 2003 for a review) hypothesizes that depression and anxiety contain common and distinct features of temperament/personality dimensions. According to the model, both depression and anxiety are posited to be characterized by high Negative Affectivity (NA), which has been described as sensitivity to negative stimuli. However, depression is also posited to be characterized by low Positive Affectivity (PA), which encompasses sensitivity to reward, while anxiety is associated with heightened autonomic arousal (i.e., racing heart, trembling, shortness of breath, dizziness).

More recent discussions have revised the tripartite model (see Mineka et al., 1998). While PA is still conceptualized as being specific to depression, and NA being common to both
depression and anxiety, theorists have argued that autonomic arousal may not be the dimension that is specific to anxiety (Greaves-Lord et al., 2007). Rather, given the heterogeneity of anxiety disorders, there may be multiple factors that distinguish particular anxiety disorders (or spectra of anxiety disorders) from depression. Unfortunately, what these factors are has not been elucidated.

Therefore, according to the tripartite model, individual differences in sensitivity to reward should be uniquely associated with family history of depression (and not anxiety disorders). However, it is less clear whether sensitivity to unpredictable/predictable threat will be associated with family history of depression and anxiety disorders or just anxiety disorders (and not depression). Part of this ambiguity stems from research indicating that anxiety disorders are heterogeneous and may be differentially related to depression (Mineka et al., 1998). For example, using the NPU-threat task, Grillon and colleagues (2009) found that, similar to PD, PTSD was associated with a heightened sensitivity to unpredictable threat, suggesting that PD and PTSD may share a common underlying mechanism. However, several factor analytic studies of Axis I disorders have shown that PTSD loads onto the same factor as MDD (and not other anxiety disorders; Krueger, 1999; Watson, 2005), suggesting that it may be more closely related to depression. Given these discrepant findings, the present study did not make any particular hypothesis as to whether sensitivity to threat was specific to risk for anxiety disorders or also associated with risk for depression.
II. METHOD

A. Participants

The sample for the present study was the same as that used in Shankman et al. (in press), which consisted of 28 individuals with current PD, 40 individuals with current MDD, 58 individuals with current PD and current MDD (i.e., comorbid) and 65 controls (total N = 191). From those 191 participants, 173 provided information on family history of psychopathology in first-degree relatives, leaving a final sample of 26 individuals with current PD, 32 individuals with current MDD, 54 individuals with current PD and current MDD (i.e., comorbid) and 61 controls. Participants that did and did not provide information on family history of psychopathology were comparable on demographic and clinical characteristics (all p’s > .18). 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 of MDD and PD as well as the interaction of MDD and PD on the variables of interest.

All diagnoses were defined by the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV; American Psychiatric Association [APA], 1994). Diagnoses were made via the Structured Clinical Interview for DSM-IV-TR (SCID; First et al., 2002) and all interview assessments were conducted by Stewart A. Shankman (S.A.S.) and advanced clinical psychology doctoral students who were trained to criterion by S.A.S. Diagnosticians were trained to criterion by viewing the SCID 101 training videos (Biometrics Research Department, New York, NY), observing 2-3 joint SCID interviews with S.A.S., and completing 3 SCID interviews (observed by S.A.S. or an advanced interviewer) where diagnoses were in agreement with the observer. To determine reliability of diagnoses, 20 SCIDs were audio recorded and
scored by a second rater blind to original diagnoses. The interrater reliability indicated perfect agreement for MDD and PD diagnoses (both Kappas = 1.00).

Depression severity was determined via the 24-item Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). Anxiety severity was determined via the Beck Anxiety Inventory (BAI; Beck, Epstein, Brown, and Steer, 1988). The BAI is a 21-item self-report questionnaire designed as a general measure of anxiety symptom severity where each item is rated on a four-point Likert scale (ranging from 0 = ‘not at all’ to 3 = ‘a lot’) according to how often the symptom has bothered the person over the previous week. 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 18 years as Shankman et al. (2007) found that it was only those with an early onset depression who exhibited an abnormal frontal EEG asymmetry during the slot task. Additionally, this inclusion criterion reduced the heterogeneity in those with an MDD diagnosis (Klein, 2008). Participants in the MDD only group were required to have no current or past history of anxiety disorder. Participants in the PD only and comorbid groups were allowed to meet criteria for additional current and past anxiety disorders, with lifetime diagnoses (current or past) including social phobia ($n = 20$), specific phobia ($n = 16$), PTSD ($n = 19$), OCD ($n = 9$), and GAD ($n = 7$). Comorbid (63.0%) and PD only (46.2%) participants did not differ in the rate of other lifetime 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 and not current; $N = 3$). Control participants were also required to have both 24-item HRSD and BAI scores of less than 8.
Participants were excluded from the study if they had a lifetime diagnosis of schizophrenia or other psychotic disorder, 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 Handedness Inventory; range of laterality quotient: +20 to +100; Oldfield, 1971). Participants were recruited through advertising in the community (e.g., flyers, Internet postings) and mental health clinics in the greater Chicago area.

B. **Family History**

Family history of psychopathology was assessed using the Family History Screen (FHS; Weissman et al., 2000), which utilizes the family history method (i.e., interview probands about family members’ psychopathology). The FHS is an interview-based measure that collects information on the lifetime history of 15 psychiatric disorders (MDD, mania, PD, GAD, agoraphobia, simple phobia, social phobia, OCD, psychosis, alcohol dependence, drug dependence, separation anxiety, conduct disorder, antisocial personality disorder, and attention-deficit hyperactivity disorder) in first-degree relatives. The present study focused on family history of depression and PD. The FHS has yielded acceptable test-retest reliability (Kappa = 0.56 for both depression and PD) and validity as determined by comparing informant family history diagnosis to best-estimate diagnoses based on direct interviews (Weissman et al., 2000).

For each disorder, the interviewer asked the proband whether any first-degree relatives had ever experienced core symptoms of the disorder across their lifetime and then asked the probands to name those family members. For example, for PD the interviewer asked if anyone on the list ever experienced a sudden spell or attack of difficulty breathing or of a rapid heartbeat. The screening question serves as a gate for the second impairment, duration, and/or exclusion question that is asked only of screen-positive individuals (e.g., PD – did they have
several attacks not caused by heart problems, etc.). For depression the interviewer asked whether anyone on the list ever felt sad, blue, or depressed for most of the time for two days or more for the initial screening question. For the second impairment, duration, and/or exclusion question the interviewer asked whether this occurred independent of physical illness or mourning of a death.

Each family member was scored on a two-point scale: 0 – participant answered ‘no’ to the initial screening question for that family member, or participant answered ‘yes’ to the initial screening question, but ‘no’ to the impairment, duration, and/or exclusion question; 1 – participant answered ‘yes’ to the initial screening question and the impairment, duration, and/or exclusion question for that family member.

C. **Procedure**

Participants completed the following experimental tasks designed to measure sensitivity to threat (NPU-threat task) and reward (slot 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.

1. **NPU-threat task and startle recording**

Participants first completed a 2.5-minute baseline task where they were presented with 9 acoustic startle stimuli. This allowed participants to habituate to the acoustic noise probes to prevent initial exaggerated startle responses. Next, shock intensity was determined using a work-up procedure where participants received increasing levels of shock, until they reached a level they described as ‘highly annoying but not painful.’ Shock level was determined ideographically to be consistent with prior studies (Grillon et al., 2004) and to ensure that subjects experienced the shocks as aversive. Shocks were 40-ms in duration, and were
administered to the wrist of the participant’s non-dominant hand. 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 groups did not differ in mean shock level ($p$’s > .38).

The NPU-threat task was modeled after that used by Grillon and colleagues (Grillon et al., 2004, 2006; Schmitz and Grillon, 2012) and included three within-subjects conditions: no shock (N), predictable shock (P), and unpredictable shock (U; see Figure 1). 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 visual cue was presented four times. The interstimulus intervals (ISIs; i.e., time between cues) 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). The time interval between a shock and the following startle probe was always greater than 10-s, which ensured that the subsequent startle response was never affected by an immediately preceding shock.

The experiment consisted of two recording blocks, with a 5-minute rest period between blocks. Each block consisted of two presentations of each 90-s condition, during which the respective cue appeared four times, in the following orders (counterbalanced): PNUNPU or UPNUNP. All participants received 12 electric shocks (6 during P and 6 during U), and 72 startle probes (24 during N, 24 during P, and 24 during U) during the countdown and ISI (with an equal number of startle probes occurring during the countdown and ISI).
After each block of trials, participants rated their level of anxiousness during the cue and ISI for each condition on a scale ranging from 1 (Not at all) to 7 (Extremely). Participants also rated how intense, annoying, and anxiety provoking the shocks were on a scale ranging from 1 (Not at all) to 7 (Extremely), and the degree to which they would avoid the shocks, on a scale ranging from 1 (Would definitely not avoid) to 7 (Would definitely avoid).

Experiment stimulation was presented using PSYLAB (Contact Precision Instruments, London, UK) and electromyography (EMG) was recorded with Neuroscan 4.4 (Compumedics, Charlotte, NC). The acoustic startle stimulus was a 40-ms duration, 103 dB burst of white noise with near instantaneous rise time presented binaurally through headphones. The startle blink reflex was measured from two 4-mm Ag/AgCl electrodes placed over the orbicularis oculi muscle below the right eye, and was collected with a bandpass filter of DC-200 Hz at a sampling-rate of 1000 Hz. As per published guidelines (Blumenthal et al., 2005), one electrode was placed 1 cm directly below the pupil and the other approximately 1 cm lateral. The ground electrode was located at the frontal pole (FPZ) of the EEG cap.

Blinks were scored according to guidelines provided by Blumenthal et al. (2005). Startle EMG was rectified and then smoothed using an FIR filter (low pass cutoff of 40 Hz). Peak amplitude of the blink reflex was determined in the 20-100 ms time frame following the startle probe onset relative to baseline (average baseline EMG level for the 50-ms preceding the startle probe onset). Blinks were scored as non-responses if EMG activity during the 20-150-ms post-stimulus time frame did not produce a blink peak that was visually differentiated from baseline activity. All analyses were conducted using blink magnitude (i.e., condition averages include values of 0 for non-response trials), as this is a more conservative estimate of blink response (Blumenthal et al., 2005). Of note, however, is that similar results were obtained using
amplitude and raw scores. Blink magnitudes were also standardized within-subjects using $t$-scores, which reduces the influence of outlier blink responses. $T$-scoring blinks also provides for better comparison between-subjects, as changes in blink magnitude amongst ‘big blinkers’ can be better compared to changes in blink magnitude amongst ‘small blinkers.’ 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 (i.e., $N_{ISI}$, $N_{Cue}$, $P_{ISI}$, $P_{Cue}$, $U_{ISI}$, $U_{Cue}$) 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). Participants who were included vs. excluded from analyses did not differ on any demographic or clinical characteristics.

2. **Slot task and EEG recording**

Participants completed a bogus computerized slot machine game (see Figure 2), similar to the one used in Shankman et al. (2007). The game consisted of three reels of numbers and fruit spinning simultaneously for exactly 11-s. The game consisted of 72 spins, which were divided into three different payoff situations— win (W), loss (L), and no incentive (NI). The L condition was included to keep the participant engaged in the task, based on results from pilot testing revealing that a win in the R condition was more exciting if there was an L condition during the task as well. Therefore, there were 30 trials in the R and NI conditions and only 12 trials in the L condition. The 72 trials were presented in a pseudo-random order in which there were never more than 2 consecutive trials of similar type or outcome. Participants began the game with $2.00 in the bank and were notified of the specific payoff situations prior to each trial (i.e., whether it was an R, L, or NI trial). To begin each trial, participants pressed a button with both thumbs to pull a lever on a computer screen that started the reels spinning. After the 11-s,
the reels stopped spinning and a message appeared on the screen notifying the participant of the outcome.

The amount of money won on any single trial varied from $0.50 to $3.00. The parameters for the R and NI conditions were similar in that a winning spin occurred when the reels landed on three pieces of fruit (e.g., three cherries). The difference between these conditions was that participants won money if this outcome occurred during the R condition but they did not win money if it occurred during the NI condition. The participant was not penalized during the R and NI conditions when this outcome did not occur. For the L condition, participants lost money when the reels landed on three pieces of fruit.

The R condition was designed to elicit approach motivation. The NI condition served as a control for several aspects of the R condition. During both conditions, the participant was watching a slot machine game (i.e., the visual input was the same). In addition, the participant was anticipating an outcome, though in the NI condition the outcome did not have monetary implications.

Unbeknown to the participant, the slot machine program was manipulated so that half of the two payoff situations landed on three pieces of fruits. There were thus six possible outcomes, consisting of 15 trials each for the R and NI conditions: R–win money, R–do not win money, NI–win (but no money), and NI–do not win money; and 6 trials each for the L conditions: L–lose money, L–do not lose money. Participants were told that the trials were in a random order to reduce the likelihood that they would perceive that they had control over the outcome of each trial. They were instructed to sit still and focus their gaze on the game. Participants were allowed to take breaks to rest their eyes between trials and were given longer breaks as needed. The task was divided into three blocks of trials (approximately 10-11 minutes
each), and participants were given a 5-minute break in between each block. At the end of the 72 trials, all participants were given their winnings ($12) in cash.

At the end of the first and second block of trials, for each type of trial (W, L, NI) participants rated how excited they were while the reels were spinning on a scale ranging from 1 (Not at all) to 7 (Extremely).

EEG was recorded in an electrically-shielded, sound-attenuated booth. Electrodes were placed according to a modified version of the 10–20 system (Sharbrough et al., 1991). EEG was recorded from 64 electrodes to measure brain activity over the entire head using a stretch-lycra electrode cap (tin electrodes): two homologous pairs (FP1/FP2; AF3/AF4) and one midline electrode (FPZ) in the prefrontal region, four homologous pairs (F7/F8; F5/F6; F3/F4; F1/F2) and one midline electrode (FZ) in the frontal region, twelve homologous pairs (FT7/FT8; FC5/FC6; FC3/FC4; FC1/FC2; T7/T8; C5/C6; C3/C4; C1/C2; TP7/TP8; CP5/CP6; CP3/CP4; CP1/CP2) and three midline electrodes (FCZ; CZ; CPZ) in the central region, and nine homologous pairs (P7/P8; P5/P6; P3/P4; P1/P2; PO7/PO8; PO5/PO6; PO3/PO4; CB1/CB2; O1/O2) and three midline electrodes (PZ; POZ; OZ) in the posterior region. Two pairs of electrodes (VEOG and HEOG) were used to determine artifacts due to vertical eye movement (e.g., blinks) and lateral eye movement, respectively. Specifically, VEOG electrodes were placed at right supra- and infra-orbital sites to monitor for eye blinks and vertical eye movements and HEOG electrodes were places on the right- and left-outer canthi to monitor horizontal eye movements. The ground electrode was at the frontal pole (FPZ) and the online reference was near the vertex (Cz).

Offline, data were re-referenced to left and right mastoid (i.e., ‘linked mastoids’ reference) data collected during the task. Electrode impedances were under 5000 ohms.
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. A PC-based EEG acquisition system (Neuroscan
4.4) acquired and digitized the data continuously at a rate of 1000 Hz.

Continuous EEG from the 11-s spinning interval was segmented into consecutive
1.024-s epochs every 0.512-s (50% overlap). Data were then examined for evidence of amplifier
saturation. After referencing to a linked mastoid reference offline and then applying a baseline
correction, epochs contaminated by blinks, eye movements, and movement related artifacts were
excluded from analyses by direct visual inspection of the raw data. This method of dealing with
artifacts has been shown to preserve spectral power across bands better than the widely used
method of electrooculogram correction (Somsen and van Beek, 1998). The EEG was tapered
over the entire 1.024-s epoch by a Hanning window to suppress spectral side lobes. Artifact-free
data, which were attenuated at the beginning and end of an epoch, were recovered in adjacent
(overlapping) epochs. 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., 1997; Henriques and Davidson, 1990), the alpha band was defined as
7.81–12.70 Hz and used as an inverse measure of regional brain activity. EEG asymmetry was
calculated by subtracting the natural log transformed alpha power in the left electrode from its
homologous right hemisphere electrode (i.e., F8- F7).

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
(i.e., F3, F4, F5, F6, F7, F8) in the NI or R condition, leaving a final sample of 156 (27 MDD
only, 24 PD only, 48 comorbids, and 57 controls). To determine whether groups and/or conditions differed in the number of EEG epochs that were accepted, a three-way mixed measures analysis of variance (ANOVA) was conducted with Condition (NI vs. R) as the within-subjects factor and Depression Status (Present vs. Absent) and Panic Status (Present vs. Absent) as between-subjects factors. Results indicated a main effect of Condition, $F(1, 152) = 25.95, p < .001, \eta_p^2 = .15$, such that the R condition ($M = 363.74, SD = 116.91$) had more accepted epochs relative to the NI condition ($M = 345.06, SD = 115.12$) condition, but there were no group differences in accepted EEG epochs (all $p$’s > .15).

D. **Data analysis**

Group differences in demographics and clinical characteristics were examined using a Pearson’s $\chi^2$ test for sex, ethnicity, lifetime alcohol use disorder, lifetime drug abuse/dependence disorder, and current psychiatric medication use. Group differences in proband age, education, GAF, HRSD, and BAI were examined using a 2(Depression Status: Present vs. Absent) X 2(Panic Status: Present vs. Absent) repeated measures ANOVA.

There are several ways to examine family history data. The most sophisticated approach is to examine each relative’s data, taking into account that each relative is nested within a family (i.e., each family member’s data is not independent) and conduct a random coefficients analysis (cf. Klein et al., 2004). While this may have been possible for family history of depression, only two families had more than one relative with PD. Thus, for PD this would have been largely equivalent to examining family history dichotomously (i.e., no family members with disorder vs. at least one family member with disorder). Additionally, examining each family member’s data using the family history approach does not take into account the fact that the proband may not be equally familiar with each family member’s psychiatric history. Therefore, we took a more
conservative approach and defined family history of depression and PD dichotomously as Absent (i.e., proband had no first-degree family member with the disorder) vs. Present (i.e., proband had at least one first-degree family member with the disorder). This approach is consistent with findings from a recent investigation that compared multiple approaches toward combining family history scores (i.e., dichotomous, density of family members, etc.), and found that for disorders with greater prevalence (e.g., depression and anxiety) the strength of the association between the different types of family history definitions and proband diagnosis was comparable (Milne et al., 2008).

Group differences in family history of PD (Present vs. Absent) and depression (Present vs. Absent) were examined using sequential logistic regression with age and sex entered in block 1, Depression Status (Present vs. Absent) and Panic Status (Present vs. Absent) entered in block 2, and Depression Status X Panic Status entered in block 3. Family history of PD and depression were the dependent variables in these analyses. If Depression Status X Panic Status predicted family history of psychopathology, it was followed-up by conducting separate logistic regression analyses in which diagnosis was dummy coded.

Before examining whether threat and reward sensitivity were associated with family history of psychopathology, the present study conducted a manipulation check to determine whether the NPU-threat and slot tasks affected psychophysiology and subjective responses in the expected directions. For the NPU-threat task, startle and subjective anxiety responding were examined using a Condition (N, P, U) by Cue (Cue vs. ISI) within-subjects ANOVA. Condition X Cue interactions were followed-up by conducting separate repeated measures ANOVAs (N vs. P vs. U) for each level of Cue. Similarly, a manipulation check on frontal EEG activity was conducted using a Condition (R vs. NI) by Hemisphere (Left vs. Right) by Region (F3/4, F5/6,
F7/8) within-subjects ANOVA. Significant Condition X Hemisphere X Region three-way interactions were followed-up by conducting separate Condition X Hemisphere repeated measures ANOVAs for each region. Condition X Hemisphere interactions were follow-up by conducting a Condition repeated measures ANOVA on EEG asymmetry (Right Hemisphere - Left Hemisphere). Subjective excitement was examined using a one-way repeated measures ANOVA on Condition (NI vs. R).

To examine whether sensitivity to threat/reward was associated with family history of psychopathology, startle and EEG scores were first z-transformed in order to directly compare odds ratios between independent variables. Next, separate sequential logistic regression analyses were conducted on family history of PD (Present vs. Absent) and depression (Present vs. Absent), with age and sex entered in block 1 and startle/subjective anxiety or EEG/subjective excitement entered as a continuous independent variable in block 2.

Finally, to examine whether sensitivity to threat/reward was associated with family history of psychopathology independent of current DSM diagnosis, proband diagnosis (Depression Status and/or Panic Status) was also z-transformed in order to be directly compared to threat/reward sensitivity. Next, separate sequential logistic regression analyses were conducted with age and sex entered in block 1, proband diagnosis entered in block 2, and startle/subjective anxiety or EEG/subjective excitement entered as a continuous independent variable in block 3.
III.   RESULTS

A.   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 $p’s > .10$). As expected, groups differed on their GAF scores with control participants scoring higher than MDD only, PD only, and comorbid participants, and PD only participants scoring higher than MDD only and comorbid participants, who did not differ. Groups also differed on their HRSD scores with control participants scoring lower than the MDD only, PD only, and comorbid participants, and PD only participants scoring lower than MDD only and comorbid participants, who did not differ. Finally, groups differed on their BAI scores with control participants scoring lower than the MDD only, PD only, and comorbid participants, and MDD only participants scoring lower than comorbid participants at a trend level, while PD only and MDD only participants did not differ and PD only and comorbid participants did not differ.

MDD only and comorbid participants did not differ in age of onset of first depressive disorder. However, comorbid participants had an earlier age of onset of first anxiety disorder relative to PD only participants. MDD only, PD only, and comorbid participants had greater rates of lifetime alcohol use disorder relative to control participants, but did not differ from each other. Finally, for both lifetime substance use disorder and current psychiatric medication use, MDD only, PD only, and comorbid participants had greater rates relative to controls, and comorbid participants had greater rates relative to PD only participants, while MDD only and PD only and MDD only and comorbid participants did not differ. Given these diagnostic group differences, lifetime substance use disorder, lifetime alcohol use disorder, and current psychiatric medication
use were included as independent variables in all subsequent analyses involving Depression Status and/or Panic Status.

B. **Family History of Psychopathology**

Table I (bottom) lists rates of family history of depression and PD across proband diagnosis. For family history of depression, results indicated a main effect of Depression Status, such that probands with MDD (MDD only and comorbid) were more likely to have at least one first-degree relative with a lifetime history of depression compared to non-MDD participants (controls and PD only), OR = 4.01 (95% CI = 1.96 – 8.17), *p* < .001. Neither the main effect for Panic Status, OR = 1.11 (95% CI = 0.55 – 2.23), *ns*, nor the interaction of Depression Status by Panic Status, OR = 0.54 (95% CI = 0.13 – 2.20), *ns*, were associated with family history of depression.

For family history of PD, results indicated a main effect for Panic Status, OR = 2.83 (95% CI = 1.19 – 6.71), *p* < .05, which was qualified by a Depression Status by Panic Status interaction, OR = 0.16 (95% CI = 0.03 – 0.93), *p* < .05. Follow-up analyses indicated that MDD only, OR = 5.26 (95% CI = 1.25 – 22.10), *p* < .05, PD only, OR = 8.56 (95% CI = 2.04 – 35.84), *p* < .01, and comorbid participants, OR = 7.16 (95% CI = 1.93 – 26.57), *p* < .01, were more likely to have at least one first-degree relative with a lifetime history of PD compared to controls. However, PD only, MDD only, and comorbid participants did not differ from each other (*p*’s > .44).

C. **NPU-Threat Task Manipulation Check**

Participants rated the shocks as moderate to extremely intense (*M* = 4.97, *SD* = 1.19), annoying (*M* = 5.21, *SD* = 1.30), and anxiety provoking (*M* = 4.97, *SD* = 1.52). Participants also rated that they would avoid receiving the shocks again to a high degree (*M* = 5.58, *SD* = 1.44).
Thus, the shocks had their intended effect of being aversive. Shock ratings did not differ between diagnostic groups (all $p$’s > .35).

Figure 3 (top) displays means (and standard errors) for startle magnitude $t$-scores across Conditions and Cues. Results indicated main effects of Condition, $F(2, 328) = 453.30$, $p < .001$, $\eta_p^2 = .73$, and Cue, $F(1, 164) = 37.43$, $p < .001$, $\eta_p^2 = .19$, and a Condition X Cue interaction, $F(2, 328) = 40.29$, $p < .001$, $\eta_p^2 = .20$. The Condition X Cue interaction was followed-up by conducting separate repeated measures ANOVAs (N vs. P vs. U) for each level of Cue (i.e., cue and ISI). During the cue, startle magnitude differed among the conditions, $F(2, 328) = 311.39$, $p < .001$, $\eta_p^2 = .66$, due to greater startle during the P Cue and U Cue relative to the N Cue, $F(1, 164) = 504.93$, $p < .001$, $\eta_p^2 = .56$; $F(1, 164) = 419.98$, $p < .001$, $\eta_p^2 = .72$, respectively, and greater startle during the P Cue relative to U Cue, $F(1, 164) = 7.56$, $p < .01$, $\eta_p^2 = .04$. Startle magnitude during the ISI also differed among the conditions, $F(2, 328) = 288.99$, $p < .001$, $\eta_p^2 = .64$, due to greater startle during the P ISI and U ISI conditions relative to the N ISI condition, $F(1, 164) = 389.59$, $p < .001$, $\eta_p^2 = .70$; $F(1, 164) = 531.07$, $p < .001$, $\eta_p^2 = .76$, respectively, and greater startle during the U ISI relative to P ISI condition, $F(1, 164) = 39.17$, $p < .001$, $\eta_p^2 = .19$.

Figure 3 (bottom) also displays means (and standard errors) for subjective anxiety across different levels of Condition and Cue. Similar to startle magnitude, results indicated main effects of Condition, $F(2, 328) = 381.50$, $p < .001$, $\eta_p^2 = .70$, and Cue, $F(1, 164) = 104.86$, $p < .001$, $\eta_p^2 = .39$, and a Condition X Cue interaction, $F(2, 328) = 93.29$, $p > .001$, $\eta_p^2 = .36$. Follow-up analyses indicated that during the cue, subjective anxiety differed among the conditions, $F(2, 328) = 369.70$, $p < .001$, $\eta_p^2 = .69$, due to greater subjective anxiety during the P Cue and U Cue conditions relative to the N Cue condition, $F(1, 164) = 430.80$, $p < .001$, $\eta_p^2 = .72$; $F(1, 164) = 416.21$, $p < .001$, $\eta_p^2 = .72$, respectively, and greater subjective anxiety during the U Cue relative
to P Cue condition, $F(1, 164) = 9.15, p < .01, \eta_p^2 = .05$. Subjective anxiety during the ISI also differed among the conditions, $F(2, 328) = 288.32, p < .001, \eta_p^2 = .64$, due to greater startle during the P ISI and U ISI conditions relative to the N ISI condition, $F(1, 164) = 173.42, p < .001, \eta_p^2 = .51; F(1, 164) = 449.41, p < .001, \eta_p^2 = .73$, respectively, and greater subjective anxiety during the U ISI relative to P ISI condition, $F(1, 164) = 163.36, p < .001, \eta_p^2 = .50$.

D. **Slot Task Manipulation Check**

Figure 4 displays means (and standard errors) for frontal EEG alpha power across Conditions and Hemispheres. Results indicated main effects for Condition, $F(1, 155) = 11.22, p = .001, \eta_p^2 = .07$, and Region, $F(2, 310) = 622.27, p < .001, \eta_p^2 = .80$, and a Condition X Hemisphere interaction, $F(1, 155) = 8.46, p < .01, \eta_p^2 = .05$. Follow-up analyses indicated that frontal EEG asymmetry (i.e., increased left [reduced alpha] relative to right activation) was greater during the R relative to NI condition, $F(1, 155) = 8.46, p < .01, \eta_p^2 < .05$. Since there was no Condition X Hemisphere X Region three-way interaction, $F(2, 310) = 1.06 ns, \eta_p^2 < .01$, the F3/4, F5/6, and F7/8 asymmetry scores were averaged together for all subsequent analyses. Finally, as expected the R condition elicited more subjective excitement while the reels were spinning relative to the NI condition, $F(1, 144) = 296.22, p < .001, \eta_p^2 = .67$.

E. **Was Threat Sensitivity Associated with Family History of PD?**

1. **Startle**

The present study first examined whether startle magnitude during the N condition was associated with family history of PD. Results indicated that neither startle during the N ISI, OR = 1.02 (95% CI = 0.69 – 1.49), ns, or N Cue, OR = 0.80 (95% CI = 0.55 – 1.16), ns, was associated with family history of PD. Therefore, change scores were computed for both the P (i.e., P Cue – N Cue) and U (i.e., U Cue – N Cue, U ISI – N ISI) threat conditions that represented
response potentiation from the N condition. Additionally, startle potentiation scores during the U condition (ISI and cue) were averaged together 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 (see top of Figure 3).

Table 2 lists odd ratios (and 95% CIs) for the analyses predicting family history. Results indicated that startle potentiation while anticipating an unpredictable threat was associated with family history of PD, such that heightened startle to an unpredictable threat was associated with a greater likelihood having at least one first-degree relative with a lifetime history of PD. Startle potentiation to P Cue was not associated with family history of PD, suggesting that the effect was specific to unpredictable threat.

2. **Subjective anxiety**

Similar to startle, subjective anxiety during the N ITI, OR = 1.11 (95% CI = 0.77 – 1.60), ns, and N Cue, OR = 1.30 (95% CI = 0.91 – 1.87), ns, was not associated with family history of PD. Therefore, change scores were computed for both the P and U threat conditions, and U potentiation scores were averaged together given that they did not differ (see bottom of Figure 4). Neither subjective anxiety potentiation during the P, OR = 0.86 (95% CI = 0.58 – 1.27), ns, or the U, OR = 0.95 (95% CI = 0.64 – 1.41), ns, threat condition was associated with family history of PD.

F. **Was Reward Sensitivity Associated with Family History of Depression?**

1. **EEG**

The present study first examined whether frontal EEG asymmetry during the N condition was associated with family history of depression. Results indicated that frontal EEG asymmetry during the NI condition was not associated with family history of depression OR =
Therefore, change scores were calculated by subtracting the NI asymmetry from the R asymmetry (i.e., R [Right Alpha Power – Left Alpha Power] – NI [Right Alpha Power – Left Alpha Power]), where greater values indicated a greater sensitivity to reward (and smaller values indicated a reduced sensitivity to reward). Logistic regression analyses indicated that frontal EEG asymmetry 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 a lifetime history of depression.

2. **Subjective excitement**

Subjective excitement during the NI condition was not associated with family history of depression, OR = 0.99 (95% CI = 0.80 – 1.23), ns; therefore, a change score was computed for subjective excitement. Results indicated that subjective excitement potentiation was not associated with family history of depression, OR = 1.03 (95% CI = 0.86 – 1.24), ns.

G. **Specificity of Associations**

To examine the specificity of the associations between sensitivity to threat/reward and family history of PD/depression, the present study also examined whether sensitivity to threat was associated with family history of depression, and whether sensitivity to reward was associated with family history of PD (see Table 2). Results indicated that startle potentiation during the P and U conditions were not associated with family history of depression. Similarly, frontal EEG asymmetry was not associated with family history of PD. Thus, startle potentiation while anticipating U threat was uniquely associated with family history of PD, whereas frontal EEG asymmetry while anticipating reward was uniquely associated with family history of depression.
H. **Was Threat/Reward Sensitivity Associated with Family History Independent of Proband Diagnosis?**

Finally, to examine whether sensitivity to U threat and reward were associated with family history of PD and depression independent of proband diagnosis, respectively, the present study conducted a sequential logistic regression with both proband diagnosis and psychophysiology measure (i.e., U threat startle potentiation/frontal EEG asymmetry) entered as independent variables (see Tables 3 and 4). For U threat sensitivity, results indicated that U startle potentiation was associated with family history of PD independent of proband PD diagnosis. Similarly, for reward sensitivity results indicated that frontal EEG asymmetry was associated with family history of depression independent of proband MDD diagnosis.
IV. Discussion

The present study examined whether two proposed mechanisms of anxiety (increased sensitivity to threat) and depression (decreased sensitivity to reward) were associated with a well-established validator of risk - family history. Specifically, individuals diagnosed with PD and/or MDD and healthy controls were interviewed about their family history of psychopathology using the family history method. Following this, participants completed two experimental tasks designed to assess sensitivity to predictable vs. unpredictable threat (measured via startle potentiation) and reward (measured via frontal EEG asymmetry). We examined whether sensitivity to threat was associated with family history of PD, sensitivity to reward was associated with family history of depression, and sensitivity to threat/reward continued to be associated with family history of psychopathology independent of current DSM diagnosis. Finally, the present study also determined the specificity of these associations by examining whether sensitivity to threat was associated with family history of depression and sensitivity to reward was associated with family history of PD.

The present study found that individual differences in threat and reward sensitivity were uniquely associated with family history of PD and depression, respectively. Specifically, heightened startle potentiation while anticipating unpredictable (but not predictable) threat was associated with increased familial liability for PD (but not depression) in first-degree relatives. In addition, a greater left frontal EEG asymmetry while anticipating reward was associated with a decreased familial liability for depression (but not PD) in first-degree relatives. 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 are uniquely associated with familial risk for PD and depression, respectively, and provide incremental validity over and above the traditional DSM diagnosis.

A. **Mechanisms of Dysfunction**

1. **Heightened sensitivity to unpredictable threat and PD**

   PD is a condition characterized by periods of intense fear (i.e., panic attacks) and anticipatory anxiety (i.e., concerns about future panic attacks). Predictability is one feature of aversive stimuli that has been shown to differentiate the states of fear (elicited by predictable threat) and anxiety (elicited by unpredictable threat). Thus, it is possible that PD would be associated with both a hypersensitivity to predictable and unpredictable threat. Indeed, in a recent investigation using the NPU-threat task, Shankman and colleagues (in press) found that PD was associated with heightened startle responding to predictable and unpredictable threat. Interestingly though, results from the present study indicated that only heightened startle responding to unpredictable (and not predictable) 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 is 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 is specific to those currently experiencing PD. This is somewhat speculative, so further research is needed to determine whether heightened sensitivity to unpredictable threat is also found in other ‘at risk’ individuals (e.g., those in remission from PD, those who later develop PD, etc.).
Grillon and colleagues (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 the repeated experience of un-cued, ‘out of the blue’ panic attacks. In turn, the acquired heightened sensitivity to unpredictable threat contributes to the development, maintenance, and worsening of PD because the associated anticipatory anxiety potentiates subsequent panic symptoms (Bouton, Mineka, and Barlow, 2001). In the second explanation, heightened sensitivity to unpredictable threat is viewed as a trait-like vulnerability factor for the development of 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 has experienced a panic attack, 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. These two explanations differ in that the former views hypersensitivity to unpredictable threat as a consequence of experiencing un-cued panic attacks, whereas the latter views the hypersensitivity as a pre-existing risk factor for the development of PD.

Results from the present study are 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, even in those who had never been diagnosed with an anxiety disorder in their lifetime (i.e., the variance left over after the removal of proband PD diagnosis), heightened startle potentiation to unpredictable threat still indexed risk for PD. Consistent with the vulnerability hypothesis, Pine et al. (2005) found that non-affected children and adolescents of parents with PD exhibited increased anticipatory anxiety to an un-cued (i.e., unpredictable) 5% CO₂
challenge, but had a normal response to the acute (i.e., predictable) challenge. Additionally, Grillon, Dierker, and Merikangas (1998) found that male adolescents of parents with anxiety disorders (including PD) exhibited greater startle potentiation while anticipating an unpredictable aversive stimulus relative to male adolescents of control parents.

2. **Reduced sensitivity to reward in MDD**

Reduced sensitivity to reward has long been considered to be one of the fundamental deficits of depression (Klein, 1987; Meehl, 1975), and numerous research findings have supported this theory (Henriques and Davidson, 2000; Henriques et al., 1994; Pizzagalli et al., 2005). Research has also indicated that approach motivation and sensitivity to reward involve the left frontal cortex (Gainotti, 1972; Luria, 1973; Robinson et al., 1983, 1984; Sackheim et al., 1982), and thus it has been hypothesized that depression would be associated with a hypoactive left frontal cortex (Davidson et al., 2002). Consistent with this hypothesis, several studies have found an abnormal frontal EEG asymmetry (characterized by reduced left relative to right frontal brain activation) in depressed individuals (Bruder et al., 1997; Henriques and Davidson, 1991).

Research has also indicated that non-depressed individuals at risk for depression exhibit an abnormal frontal EEG asymmetry. For example, several studies have found an abnormal frontal EEG asymmetry in the children of depressed relative to non-depressed mothers (Dawson, Frey, Panagiotides, Osterling, and Hessl, 1997; Field, Fox, Pickens, and Nawrocki, 1995; Jones, Field, Fox, Lundy, and Dvalos, 1997; Tomarken et al., 2004) and in individuals in remission from depression (Gotlib et al., 1998; Henriques and Davidson, 1990; Stewart et al., 2010). Given these findings, an abnormal frontal EEG asymmetry has been postulated to be a biobehavioral marker for depression (Coan and Allen, 2004).
However, as discussed above, one limitation of this research has been the reliance on measuring frontal EEG asymmetry while at rest. The present study adopted a capability model and measured EEG asymmetry during an approach-related context. Results from the present study extend other EEG asymmetry studies that have also taken a capability approach (Coan et al., 2006; Shankman et al., 2007) by examining whether the marker is 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, even within those who had never been diagnosed with depression in their lifetime (i.e., the variance left over after the removal of proband MDD diagnosis), frontal EEG asymmetry still indexed risk for depression. Overall, results from the present study suggest that reduced sensitivity to reward may index vulnerability for depression.

B. Diagnostic Categories and RDoC

There are several advantages and disadvantages to the DSM categorical approach toward diagnosing mental illness. For example, the employment of DSM categories has dramatically improved diagnostic reliability compared to the pre-DSM-III era (Spitzer and Fleiss, 1974). Additionally, decades of research that have used the DSM categories have elucidated important findings regarding the course (e.g., recovery and relapse), pathophysiology, and treatment response. However, there are still several problems with the DSM categorical approach, such as heterogeneity within categories, comorbidity across categories, and the reliance on overt clinical signs and symptoms. These findings have left many questioning whether the DSM approach is the most valid way to conceptualize mental illness.

The recent RDoC initiative may eventually provide a new nosological framework for mental illness (Insel et al., 2010; Sanislow et al., 2010). Specifically, RDoC aims to identify core
mechanisms of dysfunction that can be studied across multiple units of analysis (i.e., genes, circuits, behavior) which would ideally (someday) lead to an etiologically based system rather than one based on overt symptoms. In addition, RDoC aims to take a dimensional approach toward psychopathology, rather than making dichotomies between ‘abnormal’ and ‘normal’ functioning. In recent RDoC workshops on negative and positive valence systems, responses to acute threat (fear), potential harm (anxiety), and reward valuation were identified as potential domains of interest (NIMH, 2011b, c). However, there has been relatively limited discussion in both the RDoC workshops and publications on whether the proposed domains are associated with risk for psychopathology. Examining whether sensitivity to unpredictable threat and reward are associated with risk is important, because if these domains are truly related to the etiological underpinnings of PD and depression, respectively, then they should also be associated with risk for the disorder. Results from the present study provide substantial evidence that at least two proposed RDoC domains (‘potential harm’ and ‘reward valuation’) are associated with risk and provide a starting point on which to begin conceptualizing a modified diagnostic system.

Another aspect of the present study that relates to the RDoC initiative is the concept of discriminant validity. Discriminant validity refers to the degree to which a measurement is not associated with that of another construct (Raulin and Lilienfeld, 1997). The few papers that have been published on the RDoC initiative have largely ignored the concept of discriminant validity amongst the proposed domains. However, given the high comorbidity between Axis I disorders, several researchers have emphasized that discriminant validity may be equally (if not more) important than determining etiology. For example, Kendell and Jablensky (2003) highlighted several reasons why understanding etiology may be a challenging endeavor (e.g., etiology is not an all-or-nothing issue and likely involves a complicated interaction of multiple factors). Kendell
and Jablensky (2003) go on to suggest that discriminant validity should perhaps be determined prior to understanding etiology, especially given that the etiology of most psychiatry disorders is still largely unknown. Thus, while the primary goal of RDoC is to identify the biological etiologies of mental disorders, determining discriminant validity of the proposed domains may be equally important, and future RDoC studies should examine multiple domains simultaneously in order to determine whether they relate to the same or different constructs.

Results from the present study suggest that heightened sensitivity to threat and reduced sensitivity to reward provide discriminant validity for PD and depression constructs, respectively. Startle potentiation to unpredictable threat was only associated with family history of PD (and not depression), and reduced sensitivity to reward was uniquely associated with family history of depression (and not PD). These results are largely consistent with the revised tripartite model (Mineka et al., 1998, Watson, 2009), which posited that low PA distinguished depression from anxiety, and that each anxiety disorder might have its own specific component that differentiates it from depression (e.g., sensitivity to unpredictable threat for PD).

C. DSM-IV Diagnosis Associated with Family History of Psychopathology

As expected, proband DSM diagnosis was associated with family history of psychopathology. Specifically, probands with MDD (MDD only and comorbids) had greater rates of depression in first-degree relatives compared to non-MDD participants (PD only and controls), but did not differ from each other. These results are consistent with the large number of studies that have shown that depression runs in families of probands with depression (Andreasen et al., 1987; Gershon et al., 1982; Klein et al., 1995, 2001; Shankman et al., 2008; Sullivan et al., 2000; Weissman et al., 1982), but not in probands with anxiety (Biederman et al., 2001; Goldstein et al., 1994; Horwath et al., 1995; Low et al., 2008b; Mendlewicz et al., 1993;
Noyes et al., 1986; Weissman et al., 1983; 1984). In addition, probands with PD (PD only and comorbids) had greater rates of PD in first-degree relatives compared to controls, consistent with previous research indicating that PD runs in the families of probands with anxiety (Hettema et al., 2001; Kendler et al., 1997; Low et al., 2008b; Merikangas et al., 1998; Shankman et al., 2008). While these findings are of course, far from novel, they do further support the validity of our family history assessment measure (FHS; Weissman et al., 2000)

D. **Task Manipulation Checks**

Across the entire sample the NPU-threat and slot tasks elicited the predicted pattern of results, adding to the validity of the tasks as measures of threat (Grillon et al., 2004; Schmitz and Grillon, 2012) and reward sensitivity (Shankman et al., 2007). Specifically, for the startle task, participants had greater startle and self-reported anxiety responding during the predictable cue and unpredictable cue and ISI relative to the predictable ISI and neutral cue and ISI. For the slot task, participants had a greater relative left frontal EEG asymmetry and self-reported excitement relative to the no incentive condition.

In contrast to the startle and EEG measures, subjective anxiety and excitement were not associated with family history of psychopathology. There are several potential explanations for the lack of association between the self-reported emotions ratings and family history of psychopathology. First, the emotions ratings may have presented demand characteristics, such that participants provided responses they thought the experiment was intended to elicit. This may also explain why previous studies utilizing the same experimental tasks did not find group differences in self-reported emotions ratings (e.g., Grillon et al., 2008, 2009; Shankman et al., 2007, Shankman et al., under review). Second, the experimental tasks may have produced a ‘strong situation’ that restricted the range of responses. Situational strength is an important factor
that has been shown to moderate the relationship between individual differences and subjective and behavioral responses (Caspi and Moffitt, 1993; Cooper and Withey, 2009; Mischel, 1977). Strong situations provide unambiguous stimuli that typically yield uniform reactions across individuals. In contrast, weak situations are more ambiguous events that attenuate the influence of the situation and increase the contribution of individual differences on subsequent responses. Within the present study, the NPU-threat and slot tasks may have been so effective in eliciting subjective anxiety and excitement, respectively, that they produced a restricted range of responses. For example, during the unpredictable threat condition of the NPU-threat task, 55.8% of participants rated their anxiety between 5 and 7 during the ISI, and 58.8% made ratings in this range during the cue. Finally, the use of retrospective emotions ratings may not have reflected participant’s true emotional experience, and an online measure of subjective responding may have produced a different pattern of results.

E. **Clinical Implications**

Results from the present study have several clinical implications. For example, heightened sensitivity to unpredictable threat and reduced sensitivity to reward were associated with familial risk across all participants, even in those with no lifetime history of psychopathology. Therefore, future studies may be able to use both as biomarkers to identify individuals who may be at risk for PD and depression and potentially intervene at earlier stages of the illness (Singh and Rose, 2009). In addition, both psychophysiological measures of sensitivity to unpredictable threat and reward provided incremental validity over and above the traditional DSM diagnosis in predicting familial risk for PD and depression, respectively. For decades researchers have longed for objective, laboratory-based measures to augment diagnostic validity and address the limitations of relying on the client’s subjective reporting of symptoms.
(cf. First and Zimmerman, 2006; Hyman, 2007). However, to date there has been little agreement on which laboratory measures should be considered. Finding objective markers that add incremental diagnostic validity is an important step, and measures such as heightened sensitivity to threat and reduced sensitivity to reward may be worth considering for PD and depression constructs, respectively. Future research is needed to determine whether these laboratory-based measures prospectively predict important outcomes, such as treatment response and patient functioning.

F. **Strengths and Limitations**

The present study had several strengths. First, DSM diagnoses were determined using the SCID, and interrater reliabilities conducted on a subset of participants indicated perfect agreement. In addition, both the ‘pure’ PD only and MDD only groups had no lifetime history of depressive or anxiety disorders, respectively. Finally, two established objective measures of threat and reward sensitivity were used, and both elicited the expected pattern of results.

The present study also had several limitations. First, family history of psychopathology was determined using the family history method, in which the proband is interviewed regarding the presence or absence of various mental disorders in first-degree relatives. The family history method has been shown to exhibit good specificity but low sensitivity (Andreasen et al., 1977, 1986; Thompson et al., 1982; Orvaschel et al., 1982); therefore, the present study may have underestimated the prevalence of psychopathology in first-degree relatives. Second, 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., late onset depression). Third, PD participants were allowed to meet criteria for other current and lifetime anxiety disorders, adding heterogeneity to the sample. Thus, the results may not have been due to PD specifically, but
rather anxiety disorders in general. However, only requiring one anxiety disorder may have resulted in a less representative sample given the large comorbidity among anxiety disorders (Kessler, Chiu, Demler, and Walters, 2005). Finally, participants were allowed to be taking psychiatric medication; however, were still significant when controlling for psychiatric medication use.

G. 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 were still associated with familial risk even after controlling for proband DSM diagnosis, suggesting that each measure added incremental validity. These results suggest that adding objective measures of the core, underlying pathology may improve diagnostic validity. Future research is needed to determine whether heightened sensitivity to unpredictable threat and reduced sensitivity to reward also indicate risk for other Axis I disorders.
Table 1.

**Participant Demographics, Clinical Characteristics, and Family History of Psychopathology**

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 61)</th>
<th>MDD (n = 32)</th>
<th>PD (n = 26)</th>
<th>Comorbids (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years; SD)</td>
<td>32.5 (13.5)</td>
<td>31.3 (12.7)</td>
<td>34.2 (13.3)</td>
<td>35.6 (10.9)</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>59.0%</td>
<td>68.8%</td>
<td>61.5%</td>
<td>68.5%</td>
</tr>
<tr>
<td>Race (% Caucasian)</td>
<td>42.6%</td>
<td>43.8%</td>
<td>42.3%</td>
<td>48.1%</td>
</tr>
<tr>
<td>Education (years; SD)</td>
<td>15.4 (2.3)</td>
<td>14.6 (2.0)</td>
<td>15.2 (2.2)</td>
<td>14.6 (2.5)</td>
</tr>
<tr>
<td><strong>Clinical variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global Assessment of Functioning (GAF; SD)</td>
<td>88.9 (7.5)</td>
<td>53.6 (8.2)</td>
<td>58.5 (9.0)</td>
<td>52.1 (6.5)</td>
</tr>
<tr>
<td>Hamilton Rating Scale of Depression (HRSD; SD)</td>
<td>1.5 (1.8)</td>
<td>24.5 (8.6)</td>
<td>8.6 (7.5)</td>
<td>26.1 (8.7)</td>
</tr>
<tr>
<td>Beck Anxiety Inventory (BAI: SD)</td>
<td>1.7 (2.1)</td>
<td>14.3 (11.7)</td>
<td>15.8 (12.2)</td>
<td>19.9 (13.6)</td>
</tr>
<tr>
<td>Age of onset of first depressive disorder (years; SD)</td>
<td>-</td>
<td>13.6 (3.1)</td>
<td>-</td>
<td>13.3 (4.1)</td>
</tr>
<tr>
<td>Age of onset of first anxiety disorder (years; SD)</td>
<td>-</td>
<td>-</td>
<td>20.9 (9.0)</td>
<td>16.4 (9.1)</td>
</tr>
<tr>
<td>Lifetime alcohol use disorder</td>
<td>4.9%</td>
<td>43.8%</td>
<td>30.7%</td>
<td>46.3%</td>
</tr>
<tr>
<td>Lifetime drug use disorder</td>
<td>0.0%</td>
<td>31.3%</td>
<td>19.2%</td>
<td>40.8%</td>
</tr>
<tr>
<td>Currently taking psychiatric medication</td>
<td>1.6%</td>
<td>28.1%</td>
<td>23.1%</td>
<td>46.3%</td>
</tr>
<tr>
<td><strong>Family history of psychopathology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% probands with at least one FDR with depression</td>
<td>18.0%</td>
<td>53.1%</td>
<td>26.9%</td>
<td>51.9%</td>
</tr>
<tr>
<td>% probands with at least one FDR with PD</td>
<td>4.9%</td>
<td>21.9%</td>
<td>30.8%</td>
<td>27.8%</td>
</tr>
</tbody>
</table>

*Note. Means or percentages with different subscripts across rows were significantly different in pairwise comparisons (p < .05, chi-square test for categorical variables and Tukey’s honestly significant difference test for continuous variables). SD = Standard Deviation; MDD = Major Depressive Disorder; PD = Panic Disorder; FDR = First-Degree Relative.*
Table 2.

**Logistic Regression Odds Ratios (and 95% Confidence Intervals) for Startle Potentiation and Frontal EEG Asymmetry Predicting Family History of PD and Depression.**

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Family History of PD</th>
<th>Family History of Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model 1 – Predictable Threat Sensitivity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.01 (0.98 – 1.04)</td>
<td>1.02 (0.99 – 1.04)</td>
</tr>
<tr>
<td>Sex</td>
<td>1.65 (0.71 – 3.85)</td>
<td>1.55 (0.78 – 3.10)</td>
</tr>
<tr>
<td>P Threat Startle Potentiation</td>
<td>1.28 (0.85 – 1.92)</td>
<td>1.14 (0.82 – 1.58)</td>
</tr>
<tr>
<td><strong>Model 2 – Unpredictable Threat Sensitivity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.01 (0.98 – 1.04)</td>
<td>1.02 (0.99 – 1.04)</td>
</tr>
<tr>
<td>Sex</td>
<td>1.78 (0.75 – 4.22)</td>
<td>1.55 (0.77 – 3.08)</td>
</tr>
<tr>
<td>U Threat Startle Potentiation</td>
<td>1.60 (1.03 – 2.47)*</td>
<td>1.01 (0.73 – 1.40)</td>
</tr>
<tr>
<td><strong>Model 3 – Reward Sensitivity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.01 (0.98 – 1.04)</td>
<td>1.03 (1.00 – 1.06)*</td>
</tr>
<tr>
<td>Sex</td>
<td>2.09 (0.84 – 5.23)</td>
<td>1.54 (0.74 – 3.17)</td>
</tr>
<tr>
<td>Frontal EEG Asymmetry</td>
<td>1.03 (0.69 – 1.53)</td>
<td>0.61 (0.43 – 0.88)*</td>
</tr>
</tbody>
</table>

*Note.* P threat startle potentiation was $P_{Cue} - N_{Cue}$, and U threat startle potentiation was the average of $U_{Cue} - N_{Cue}$ and $U_{ISI} - N_{ISI}$. Frontal EEG asymmetry was the average of the F3/4, F5/6, and F7/8 asymmetry scores where left alpha power was subtracted from right alpha power (i.e., R [Right - Left] - NI [Right - Left]). P threat startle potentiation, U threat startle potentiation, and frontal EEG asymmetry were all z-transformed for these analyses in order to directly compare odds ratios between measurements. Block 1 odds ratios (and 95% confidence intervals) for age and sex are not presented in the table. P = Predictable; U = Unpredictable; EEG = Electroencephalography; PD = Panic Disorder; ISI = Inter-Stimulus Interval; R = Reward; NI = No Incentive. + $p < .10$, * $p < .05$. 
Table 3.

Logistic Regression Odds Ratios (and 95% Confidence Intervals) for Proband Diagnosis and Unpredictable Threat Startle Potentiation Predicting Family History of PD.

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Family History of PD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Block 2</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.00 (0.97 – 1.04)</td>
</tr>
<tr>
<td>Sex</td>
<td>1.88 (0.72 – 4.94)</td>
</tr>
<tr>
<td>Psychiatric Medication</td>
<td>2.21 (0.88 – 5.53)+</td>
</tr>
<tr>
<td>Lifetime Alcohol Use Disorder</td>
<td>0.74 (0.41 – 1.32)</td>
</tr>
<tr>
<td>Lifetime Drug Use Disorder</td>
<td>1.61 (0.93 – 2.78)+</td>
</tr>
<tr>
<td>Panic Status</td>
<td>1.65 (1.02 – 2.68)*</td>
</tr>
<tr>
<td>Depression Status</td>
<td>1.35 (0.82 – 2.23)</td>
</tr>
<tr>
<td>Panic Status X Depression Status</td>
<td>0.63 (0.40 – 1.00)*</td>
</tr>
<tr>
<td><strong>Block 3</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.00 (0.97 – 1.04)</td>
</tr>
<tr>
<td>Sex</td>
<td>1.91 (0.72 – 5.08)</td>
</tr>
<tr>
<td>Psychiatric Medication</td>
<td>2.12 (0.83 – 5.39)</td>
</tr>
<tr>
<td>Lifetime Alcohol Use Disorder</td>
<td>0.71 (0.39 – 1.29)</td>
</tr>
<tr>
<td>Lifetime Drug Use Disorder</td>
<td>1.68 (0.96 – 2.94)+</td>
</tr>
<tr>
<td>Panic Status</td>
<td>1.61 (0.99 – 2.63)+</td>
</tr>
<tr>
<td>Depression Status</td>
<td>1.40 (0.84 – 2.33)</td>
</tr>
<tr>
<td>Panic Status X Depression Status</td>
<td>0.63 (0.40 – 1.00)+</td>
</tr>
<tr>
<td>U Threat Startle Potentiation</td>
<td>1.64 (1.03 – 2.62)*</td>
</tr>
</tbody>
</table>

*Note. U threat startle potentiation was the average of $U_{Cue} - N_{Cue}$ and $U_{ISI} - N_{ISI}$. Lifetime Alcohol Use Disorder, Lifetime Drug Use Disorder, Depression Status, Panic Status, and U Threat Startle Potentiation were z-transformed for these analyses in order to directly compare odds ratios between measurements. Block 1 odds ratios (and 95% confidence intervals) for age and sex are not presented in the table. U = Unpredictable; PD = Panic Disorder; ISI = Inter-Stimulus Interval. + p < .10, * p < .05.
Table 4.

Logistic Regression Odds Ratios (and 95% Confidence Intervals) for Z-Transformed Proband Diagnosis and Frontal EEG Asymmetry Predicting Family History of Depression.

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Family History of Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Block 2</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.02 (1.00 – 1.05)</td>
</tr>
<tr>
<td>Sex</td>
<td>1.53 (0.70 – 3.35)</td>
</tr>
<tr>
<td>Psychiatric Medication</td>
<td>1.45 (0.62 – 3.37)</td>
</tr>
<tr>
<td>Lifetime Alcohol Use Disorder</td>
<td>1.27 (0.78 – 2.07)</td>
</tr>
<tr>
<td>Lifetime Drug Use Disorder</td>
<td>0.91 (0.56 – 1.48)</td>
</tr>
<tr>
<td>Depression Status</td>
<td>1.88 (1.26 – 2.80)**</td>
</tr>
<tr>
<td><strong>Block 3</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.03 (1.00 – 1.06)+</td>
</tr>
<tr>
<td>Sex</td>
<td>1.66 (0.75 – 3.71)</td>
</tr>
<tr>
<td>Psychiatric Medication</td>
<td>1.30 (0.55 – 3.09)</td>
</tr>
<tr>
<td>Lifetime Alcohol Use Disorder</td>
<td>1.28 (0.77 – 2.11)</td>
</tr>
<tr>
<td>Lifetime Drug Use Disorder</td>
<td>0.92 (0.56 – 1.51)</td>
</tr>
<tr>
<td>Depression Status</td>
<td>1.82 (1.21 – 2.73)**</td>
</tr>
<tr>
<td>Frontal EEG Asymmetry</td>
<td>0.66 (0.45 – 0.96)*</td>
</tr>
</tbody>
</table>

*Note. Frontal EEG asymmetry was the average of the F3/4, F5/6, and F7/8 asymmetry scores where left alpha power was subtracted from right alpha power (i.e., R [Right - Left] - NI [Right - Left]). Lifetime Alcohol Use Disorder, Lifetime Drug Use Disorder, Depression Status and Frontal EEG Asymmetry were z-transformed for these analyses in order to directly compare odds ratios between measurements. Block 1 odds ratios (and 95% confidence intervals) for age and sex are not presented in the table. EEG = Electroencephalography; R = Reward; NI = No Incentive. + p < .10, * p < .05, ** p < .01.
Figure 1. Depiction of the NPU-threat study design. N = Neutral; P = Predictable; U = Unpredictable; ISI = Inter-Stimulus Interval; ⌧ = Startle Probe; ⚡ = Electric Shock
Figure 2. Picture of the electroencephalography (EEG) slot machine game.
Figure 3. Mean startle magnitude (top) and subjective anxiety (bottom) at different levels of Condition and Cue. Error bars represent standard error. N = Neutral; P = Predictable; U = Unpredictable; ISI = Inter-Stimulus Interval; au = arbitrary units.
Figure 4. Mean ln transformed frontal EEG alpha power at different levels of Condition and Hemisphere. ‘Left Hemisphere’ was the average EEG alpha power over F3, F5, and F7, and ‘Right Hemisphere’ was the average EEG alpha power over F4, F6, and F8. Error bars represent standard error. EEG = electroencephalography; NI = No Incentive; R = Reward; Hz = Hertz.
REFERENCES


sensitivity in individuals with panic disorder and/or depression. *Journal of Abnormal Psychology.*


Office for the Protection of Research Subjects (OPRS)
Office of the Vice Chancellor for Research (MC 670)
203 Administrative Office Building
1737 West York Street
Chicago, Illinois 60612 7227

Approval Notice
Continuing Review

July 13, 2011

Stewart Shankman, Ph.D.
Psychology
912 S. Wood Street, 4th Floor
M/C 285
Chicago, IL 60612
Phone: (312) 355-3812 / Fax: (312) 413-4122

RE: Protocol # 2005-0626
   “Emotional Processing and Physiology”

Dear Dr. Shankman:

Your Continuing Review was reviewed and approved by the Expedited review process on July 7, 2011. You may now continue your research.

Please note the following information about your approved research protocol:

Protocol Approval Period: July 7, 2011 - July 5, 2012
Approved Subject Enrollment #: 655
Additional Determinations for Research Involving Minors: The Board determined that this research satisfies 45CFR46.404, research not involving greater than minimal risk. Therefore, in accordance with 45CFR46.408, the IRB determined that only one parent's/legal guardian's permission/signature is needed
Performance Site: UIC
Sponsor: NARSAD (Nat'l Alliance for Research on Schizophrenia and Depression), Office of Social Science Research (OSSR), NIMH - National Institute of Mental Health, Department of Psychology
PAF#: 2008-00188, Not available, Not available,2008-05183
Grant/Contract No: Not available, Not available, Not available,1R21MH080689-01A2
Grant/Contract Title: Neurobehavioral processes that are common and/or specific to major depression and anxiety: an fMRI study, Not available, Not available, Anticipating reward & threat: A test of biobehavioral processes in MDD vs anxiety
Research Protocol:
   a) "Emotional Processing and Physiology", Version #6, 09/06/2010

Phone: 312-996-1711 http://www.uic.edu/depts/oVcr/oprs/ FAX: 312-413-2929

85
VITA

NAME
Brady Douglas Nelson

EDUCATION

Present
Clinical Psychology Internship, Department of Psychiatry, University of Illinois-Chicago

2008-2012
Ph.D., Clinical Psychology, University of Illinois-Chicago
Dissertation: Do Individual Differences in Reward and Threat Sensitivity Predict Family History of Psychopathology?
Committee: Stewart Shankman (Chair), Ellen Herbener, Robin Mermelstein, Mitch Roitman, and Daniel Klein.

2006-2008
M.A., Clinical Psychology, University of Illinois-Chicago
Thesis: Emotional Reactivity in Major Depressive Disorder: An Examination of the Moderating Effects of Personality and Characteristics of Depression
Committee: Stewart Shankman (Chair), Jon Kassel, and Ellen Herbener.

2001-2005
B.A., Psychology, University of Wisconsin-Madison

PEER-REVIEWED PUBLICATIONS


BOOK CHAPTERS


AWARDS/DISTINCTIONS

**2011-2012**

**UIC Chancellor’s Graduate Research Fellowship** presented by the UIC Graduate College (Total Award: $8000)

**2011**

**Smadar Levin Award for Most Outstanding Graduate Student Poster** at the 25th Annual Meeting of the Society for Research in Psychopathology, Boston, MA, September 2011

**2011**

**Excellence in Clinical Psychology Award** presented by the UIC Department of Psychology (Total Award: $500)

**2011**

**LAS PhD Student Travel Award** (Total Award: $500)

**2009**

**Clinical Preliminary Examination Passed with Commendation**, Chicago, IL

**2008-2011**

**UIC Graduate Student Council/Graduate College Travel Award** (Total Award: $500/year)

**2008-2011**

**UIC Department of Psychology Travel Award** (Total Award: $200/year)

CONFERENCE PRESENTATIONS


at the 2nd Annual University of Illinois – Chicago Student Research Forum, Chicago, IL.


at the 39th Annual Meeting of the International Neuropsychological Society, Boston, MA.


of ancestry. Poster presented at the 2012 Association for Psychological Science Annual Convention, Chicago, IL.


INVITED ADDRESSES

RESEARCH EXPERIENCE
2012-present Clinical Psychology Intern Volunteer – Phan Neuroimaging Laboratory
University of Illinois-Chicago, Department of Psychiatry

• Clinical psychology intern volunteer completing research rotation in Dr. Phan’s neuroimaging laboratory
• Processed fMRI data using SPM for a project examining neural substrates of voluntary emotion regulation
  Advisors: Luan Phan, M.D., Daniel Fitzgerald, Ph.D.

2006-2012 Graduate Research Assistant – Affective Science and Physiology Laboratory
University of Illinois-Chicago, Department of Psychology
• Primary lab experimenter in a project examining anticipation to reward and threat in individuals with depression and/or panic disorder
• Designed and programmed experimental tasks using E-Prime and PsyLab
• Processed EEG (NeuroScan), EMG (NeuroScan), fMRI (AFNI, SPM), and HRV (CardioEdit) data
  Advisor: Stewart Shankman, Ph.D.

2008-2010  Graduate Research Assistant – Herbener Research Lab
University of Illinois-Chicago, Department of Psychology and Psychiatry
• Processed fMRI data using AFNI for project examining neural correlates of short and long-term affective memory in patients with schizophrenia
  Advisor: Ellen Herbener, Ph.D.

2004-2006  Research Assistant - Laboratory for Affective Neuroscience
University of Wisconsin-Madison, Department of Psychology
• Assisted in the study design, scheduling, and running of participants in an fMRI investigation of the neural substrates of emotion regulation
• Primary lab experimenter in study investigating individual differences in startle reflex during voluntarily emotion regulation
  Advisors: Hyejeen Lee, M.A., Richard Davidson, Ph.D.

2004-2006  Research Assistant – Psychopathy Research Laboratory
University of Wisconsin-Madison, Department of Psychology
• Assisted in screening and running participants incarcerated in the Wisconsin Department of Corrections maximum-security prisons
• Primary lab experimenter in a project examining vigilance processing using EEG
  Advisor: Joseph Newman, Ph.D.

2002-2005  Research Assistant – Center for Eukaryotic Structural Genomics
University of Wisconsin-Madison, Department of Biochemistry
• Worked on project investigating protein purification and characterization
• Assisted in data entry, protein sample maintenance, experiment preparation, and liquid nitrogen drop freezing
  Advisor: Frank Vojtik, Ph.D.

CLINICAL EXPERIENCE
2012-2013  Clinical Psychology Internship
University of Illinois-Chicago, Department of Psychiatry
• Performed psychological evaluation and intervention services, including rotations in neuropsychology, health psychology, and pediatric mood disorders.
  Supervisors: Neil Pliskin, Ph.D., ABPP-CN, Susan Labott, Ph.D., ABPP-CHP, & Amy West, Ph.D.

2006-2012  Office of Applied Psychological Services
University of Illinois-Chicago, Department of Psychology
• Performed psychological services, including intake interviews, psychological assessments, individual psychotherapy, and group psychotherapy.  
**Supervisors**: Evelyn Behar, Ph.D., Gloria Balague, Ph.D., Nancy T. Dassoff, Ph.D., Audrey J. Ruderman, Ph.D., & Alicia Matthews, Ph.D.

**2009-2010**  
**Neuropsychology Externship**  
**University of Illinois-Chicago, Department of Psychiatry**  
• Performed neuropsychological assessments of outpatients using various tests, such as the WAIS-IV, CVLT-II, BVMT-R, DRS, RBANS, WCST, etc.  
**Supervisors**: Neil H. Pliskin, Ph.D., ABPP-CN & David L. Nyenhuis, Ph.D., ABPP-CN

**2010-2011**  
**Stress and Anxiety Disorders Clinic Externship**  
**University of Illinois-Chicago, Department of Psychiatry**  
• Performed psychological services, including intake interviews, individual psychotherapy, and group psychotherapy, in an outpatient setting.  
**Supervisor**: Cheryl Carmin, Ph.D.

**ATTENDED WORKSHOPS AND TRAINING**

**MMPI-2-RF: Basic Overview Webinar (2012)**. Presented by Yossef S. Ben-Porath (sponsored by Pearson Assessments).

**Performing Clinical Services with Hearing Impaired Clients (2010)**. Presented by the UIC Disability Center.


**Mindfulness-Based Cognitive Therapy and Prevention of Relapse in Major Depression (2006)**. Presented by Zindel Segal and Mark Lau at the 40th Annual Convention of the Association for Behavioral and Cognitive Therapies.


**TEACHING EXPERIENCE**

**2012**  
**Teaching Assistant – Abnormal Psychology**  
**University of Illinois-Chicago, Department of Psychology**  
• Attended lectures and graded papers (3 credit course)
2010-2012  Teaching Assistant – Practicum in Psychological Assessment  
University of Illinois-Chicago, Department of Psychology  
• Supervised 1\textsuperscript{st}–3\textsuperscript{rd} year clinical psychology graduate students in administering various psychological/neuropsychological assessments. Primary duties involved training students in administering psychological assessments, such as the WAIS-IV, D-KEFS, CVLT-II, etc. (3 credit course)

2008-2009  Teaching Assistant – Theories of Personality  
University of Illinois-Chicago, Department of Psychology  
• Attended lecture and graded papers (3 credit course)

2007, 2012  Teaching Assistant – Psychological Testing  
University of Illinois-Chicago, Department of Psychology  
• Attended lectures and graded papers (3 credit course)

2007  Teaching Assistant – Statistics for Psychology  
University of Illinois-Chicago, Department of Psychology  
• Led two weekly discussion sections and graded homework and exams (3 credit course)

2006  Teaching Assistant – Introduction to Psychology  
University of Illinois-Chicago, Department of Psychology  
• Led four weekly discussion sections and graded papers (3 credit course)

SERVICE EXPERIENCE
2010-2012  Clinical Psychology Division Liaison  
University of Illinois–Chicago, Department of Psychology  
• Worked with faculty and students on various departmental issues  
• Updated and maintained division handbook  
• Organized department sponsored speakers and events  
• Organized visiting day arrangements and activities

MEMBERSHIPS & AFFILIATIONS
Society for Psychophysiological Research  
American Psychological Association – Student Affiliate  
Division 40 – Clinical Neuropsychology  
Association for Research in Personality  
Social & Affective Neuroscience Society  
Association for Psychological Science  
Society for a Science of Clinical Psychology

AD HOC REVIEWER
Behaviour Research and Therapy  
Biological Psychology  
Journal of Abnormal Psychology
SOFTWARE COMPETENCIES
AFNI
CardioBatch
CardioEdit
E-Prime
Microsoft Office
NeuroScan
PsyLab
SecureCRT
SecureFX
SPM
SPSS