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Time Course of Threat Responding in Panic Disorder and Depression

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Abstract

Heightened sensitivity to threat is a characteristic feature of panic disorder (PD). It is also a factor that is considered to be central to PD but not major depressive disorder (MDD) – a related disorder that commonly co-occurs with PD. However, sensitivity to threat is a broad construct and it is unclear whether individuals with PD exhibit heightened initial threat reactivity, impairments in modulating their threat responding over time, or both. It is also unclear how these different facets of threat responding apply to predictable and/or unpredictable threat. The aim of the current study was to examine whether there are differences in initial threat reactivity and the time course of threat responding during predictable and unpredictable threat-of-shock in 186 adults with: 1) current PD and no history of depression (i.e., PD-only), 2) current MDD and no history of an anxiety disorder (i.e., MDD-only), 3) current comorbid PD and MDD, or 4) no lifetime history of psychopathology (i.e., controls). Threat responding was assessed using an electromyography startle paradigm. Relative to controls, individuals in the three psychopathology groups exhibited heightened initial threat reactivity to predictable and unpredictable threat and did not differ from each other. Multilevel mixed model analyses indicated that those with PD evidenced less of a decline over time in startle responding during unpredictable threat relative to those without PD. Those with MDD displayed a greater slope of decline in startle responding during predictable threat compared with those without MDD. The pattern of results suggests that there may be conceptual differences between measures of initial threat reactivity and time course of threat responding. Moreover, time course of threat responding, not initial threat reactivity, may differentiate PD from MDD.

Keywords

panic disorder; major depressive disorder; startle; time course; affective chronometry

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¹Of note, the pattern of results is identical whether the raw blink values or the square-root transformed blink values are used as dependent variables.

1. Introduction

Epidemiological data indicate that concurrent diagnoses of depression and anxiety are common (Kendler et al., 2003; Vollebergh et al., 2001). Among those with major depressive disorder (MDD), 58% have a lifetime diagnosis of any anxiety disorder (Kessler et al., 1996, 2005). The rate of comorbid depression within anxiety disorder patients is similar, though rates vary by type of anxiety disorder (Clark, 1989; Kessler et al., 1997). In all cases, comorbidity rates far exceed what would be expected by chance.

Numerous theories have attempted to explain this common co-occurrence by identifying the factors that are common to the two classes of disorders and those that are unique (see Shankman & Klein, 2003). In other words, studies have sought to delineate what traits/characteristics are related to depression *and* anxiety (i.e., shared), and what traits/characteristics are related to depression but not anxiety and vice versa (i.e., unique). The original tripartite model posited that high negative affectivity was common to both depression and anxiety, whereas low positive affectivity was unique to depression and heightened physiological arousal was unique to anxiety (Clark & Watson, 1991). Over the past two decades, there have been several revisions to the tripartite model (Mineka et al., 1998; Watson, 2009). To date, high negative affectivity is still considered shared between depression and anxiety, and low positive affectivity unique to depression. However, the unique features of anxiety disorders are unclear and it has been postulated that the traits/characteristics that differentiate one anxiety disorder from depression may be different than the traits/characteristics that differentiate another anxiety disorder from depression (Heller & Nitschke, 1998; Watson, 2009).

Along these lines, accumulating research and theory suggests that heightened threat sensitivity may be specific to panic disorder (PD) (and potentially other fear-based disorders) relative to MDD (Gorman et al., 2001; Nelson et al., 2013; Shankman et al., 2013). However, it is important to note that ‘heightened threat sensitivity’ is a broad construct and it unknown whether individuals with PD exhibit heightened initial threat reactivity, impairments in modulating their threat responding over time, or both. The majority of prior studies have collapsed across aversive events to create an average level of responding (Grillon et al., 2004; Grillon et al., 2008; Melzig et al., 2007). This approach increases reliability by averaging multiple responses, but fails to capture the pattern of responding over time (an approach called “affective chronometry” Davidson, 1998). Thus, the precise nature of dysfunctional threat responding in individuals with PD cannot be inferred.

Examining the pattern of threat responding over time may help elucidate distinct disease mechanisms that are conflated by only examining differences in average responding (Gross, 1999; Werner & Gross, 2010). Ideally, studies would allow for separate examinations of initial affective reactivity and change in responding over time, as data suggests that the two measures are different (e.g., Gorka et al., 2013; Campbell et al., 2014; Mogg et al., 2004). For example, the former may reflect initial stimulus processing, while the latter may reflect inhibitory processes (Banks et al., 2007; Phan et al., 2005).

A common approach to studying time course of responding is to examine habituation – often defined as the gradual decrease in physiological responding to a stimulus over time (Harris, 1943; Herry et al., 2010). Habituation is considered an adaptive response style to an ongoing stimulus (Groves & Thompson, 1970; Herry et al., 2010; Rankin et al., 2009). A slower rate (or lack) of response reduction is conceptualized as an index of sustained heightened vigilance (Oken et al., 2006). Roth and colleagues (1990) found that individuals with PD evidenced deficits in the rate of reduction of skin conductance responses to aversive auditory tones. More recently, it has been shown that those with PD, relative to healthy controls, exhibit increased respiratory reactivity and a lack of habituation over time in response to a panicogenic carbondioxide challenge (Blechert et al., 2010). Although considerably less work has been done examining the time course of affective processing in MDD, studies typically suggest that individuals with MDD exhibit normal rates of habituation to threatening stimuli (e.g., Taiminen et al., 2000). Taken together, the existing literature suggests that ‘heightened sensitivity to threat’ in PD patients could reflect heightened initial reactivity, deficits in the reduction of responding over time, or some combination of these. It is also possible that individuals with MDD exhibit a form of abnormal threat responding which has not been captured by traditional averaging of responses, such as increased reactivity but normal habituation.

Another important factor related to threat sensitivity that impacts responding is whether or not the threat is temporally predictable or unpredictable (Abbott et al., 1984; Grillon et al., 2008; Shankman et al., 2014). Broadly, predictable threat elicits a phasic response to an identifiable stimulus (labeled *fear*), while unpredictable threat elicits a generalized feeling of apprehension not associated with a clearly identifiable source (labeled *anxiety*; Davis, 1998; Barlow, 2000). These two types of threat have been shown to elicit qualitatively distinct aversive states (Davis, 1998; Davis et al., 2010; Grillon et al., 2006), and have overlapping, yet separable neural correlates (Alvarez et al., 2011; Davis, 2006).

In order to assess fear and anxiety responses separately, Grillon and colleagues developed the NPU-threat paradigm (Grillon et al., 2004; Schmitz & Grillon, 2012). The task includes three within-subjects conditions: 1) no threat (N; subjects are safe from aversive stimuli), 2) predictable threat (P; aversive stimuli are signaled by short duration cues), and 3) unpredictable threat (U; aversive stimuli are not signaled). Throughout conditions, startle eyeblinks in response to probes (e.g., short bursts of white noise) are recorded as indices of aversive responding (Bradley et al., 1999; Lang, 1995).

Using this paradigm (and its variants), two separate studies have demonstrated that individuals with PD evidence greater average startle responding during anticipation of threat relative to healthy controls (Grillon et al., 2008; Shankman et al., 2013) and individuals with MDD (Shankman et al., 2013). Specifically, both studies found that PD was associated with heightened startle potentiation to unpredictable threat; however, only Shankman et al. (2013) found that PD was also associated with heightened startle to predictable threat. A third study using the NPU-threat paradigm found that MDD was associated with greater startle responding across predictable, unpredictable, and no-shock conditions compared with healthy controls (Grillon et al., 2013); although, Shankman et al. (2013) did not find any association between MDD and startle responding. Thus, there have been some discrepant

findings in the literature. First, it is unclear whether PD is associated with responding to predictable *and* unpredictable threat; although, studies using other task designs suggest that PD may be related to both forms of threat (e.g., Gorman et al., 2001; Melzig et al., 2007). Second, because of the differing findings between Grillon et al. (2013) and Shankman et al. (2013), the role of MDD in threat responding is unclear.

Using startle paradigms other than NPU, it has been shown that healthy controls and individuals with a current anxiety disorder both display elevated startle potentiation when viewing unpleasant pictures; however, individuals with an anxiety disorder and comorbid depression have blunted startle (Taylor-Clift et al., 2011). Additionally, in a sample of adolescents with principal fear disorders (i.e., specific and social phobia), distress disorders (i.e., MDD, dysthymia, generalized anxiety disorder, and PTSD), and controls, Waters et al. (2014) found that those with a principal fear disorder, relative to the other two groups, exhibited greater startle during safety conditions and during early phases of explicit threat (i.e., an aversive event was possible but it would not occur for another 10-50s). Meanwhile, adolescents with principal distress disorders displayed blunted startle responding during baseline and contextual threat conditions (i.e., aversive events would happen later in the task and participants were told they would be notified of the timing) relative to individuals without principal distress disorders. These studies highlight the conflicting findings within the startle literature, and also point to the fact that the type and timing of threat may have an important impact on the pattern of results.

The aim of the current study was to examine whether there are group differences in initial threat reactivity and the time course of threat responding among individuals with PD and/or MDD. Data for this study came from Shankman et al. (2013), which reported that individuals with PD (with and without MDD) evidence heightened startle potentiation to predictable and unpredictable threat compared to individuals with MDD-only and healthy controls. As was noted above, this original study collapsed across responses to create condition averages and thus, did not separate initial reactivity and time course effects. It is hypothesized that individuals with PD (with and without MDD) will display increased initial reactivity and a lack of reduction in responses over time during both predictable and unpredictable threat relative to individuals without PD. In regards to MDD-only, the majority of existing studies suggest that individuals with MDD-only display blunted startle to unpleasant stimuli (see Vaidyanathan et al., 2009 for a review); although, in the current sample, Shankman et al. (2013) found no effect of MDD. Given this difference, and a study by Cuthbert et al. (2003) noting that depressed individuals displayed increased initial startle reactivity, we hypothesized that the MDD-only group will exhibit increased initial reactivity but a greater rate (or slope) of reduction in responses over time during both predictable and unpredictable threat relative to individuals without MDD. Lastly, because there was no impact of co-occurring MDD or PD in Shankman et al. (2013), we did not hypothesize that there would be differences in the pattern of results for individuals with co-occurring MDD and PD relative to individuals with PD-only and MDD-only.

2. Methods

The study protocol has been described in detail elsewhere (see Shankman et al., 2013). In brief, sensitivity to predictable and unpredictable threat was examined in four groups of individuals with current: (1) PD without a lifetime history of MDD ($n = 28$), (2) MDD without a lifetime history of an anxiety disorder ($n = 38$), (3) comorbid PD and MDD ($n = 56$), and (4) healthy controls with no lifetime history of Axis I psychopathology ($n = 64$). Diagnoses were made via the Structured Clinical Interview for DSM-IV (SCID; First et al., 1996). Participants in the PD-only and comorbid groups were allowed to have additional current or past anxiety disorders. Participants in the MDD-only group were required to have no current or past anxiety disorder. In addition, as part of the aims for the larger study, and in an attempt to reduce heterogeneity within depressed individuals, participants in the MDD-only and comorbid PD and MDD groups were required to have a first onset of depression or dysthymia by age 18-years. Individuals were recruited from the community and were excluded from the larger study if they had a lifetime diagnosis of a psychotic disorder, bipolar disorder, or dementia; were unable to read or write in 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). Five participants were excluded from the study due to equipment failure during the task that caused them to receive unintended startle probes.

2.1 Procedure and NPU-Threat Task

After providing written informed consent, participants were seated in an electrically shielded, sound-attenuated booth for the duration of the session. To prevent early exaggerated startle responding, participants heard 9 acoustic startle probes prior to the task. Next, a shock work-up procedure was completed in which participants received increasing levels of shock intensity until they reached a level that they described as feeling “highly annoying but not painful.” More specifically, during our instructions we specifically told participants we wanted to identify the level of shock that they would describe as “highly annoying but not painful.” To do so, we administered our lowest level of shock first (0.6 mA), inquired about the participants’ subjective rating of the shock, and gradually increased the shock level by 0.6mA, asking after each administration if the level of shock had reached the desired subjective threshold. Individual shock levels were used to ensure equality in perceived shock aversiveness (Rollman & Harris, 1987) and to be consistent with prior studies (e.g., Grillon et al., 2008). The maximum shock level a participant could achieve was 5 mA. The mean shock level was 2.2 mA ($SD = 1.3$).

Startle responding was assessed using a modified version of the NPU-threat task (see Shankman et al. 2013; Gorka et al., 2013), which included three within-subjects conditions - no shock (N), predictable shock (P), and unpredictable shock (U). Text at the bottom of the computer monitor informed participants of the current threat condition by displaying: “no shock” (N), “shock possible during square” (P), or “shock possible at any time” (U). Each condition lasted 90-s, during which an 8-s geometric cue (blue circle for N, red square for P, and green star for U) was presented four times. Different shapes were used for each condition to ensure that participants were aware of the current condition. Interstimulus

intervals (ISIs) ranged from 7 to 17-s ($M = 12.4$ -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. The shock was delivered at the end of the cue presentation (i.e., the 6th or 7th second) during the P condition. In the U condition, shocks were administered at any time (i.e., during the cue or ISI). Given that the U shocks were spread out across cue and ISI periods, there were several periods in which no shock occurred, making the U condition completely unpredictable. Startle probes were presented during the cue (2-7-s following cue onset) and ISI (4-12-s following ISI onset). Only one startle probe was delivered during each presentation of the cue or each ISI.

The task was divided into two recording blocks, separated by a rest period that was on average 3.7-mins long ($SD = 1.4$ -mins). 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). The time interval between a shock and a subsequent startle probe was always greater than 10-s to minimize startle responses from being affected by an immediately preceding shock. Of note, the average interval between a shock and subsequent startle probe were balanced across the U and P conditions.

It is important to highlight that there are several differences between the currently used version of the NPU-threat task and the original NPU-threat task described in Schmitz and Grillon (2012). Most notably, the present task includes two N-conditions within each block (so as to have equal occurrences of N, P, and U conditions) whereas the original includes three N-conditions. The original version also includes slightly longer conditions and ISIs between startle probes relative to the current version.

2.2 Startle Data Collection and Processing

Stimuli (e.g., shocks, white noise) were administered using PSYLAB (Contact Precision Instruments, London, UK) hardware and software (e.g., PSYLABTG/WN white noise generator and SHK1 shocker via Stand Alone Monitor [SAM] unit). Psychophysiological data were acquired using Neuroscan 4.4 (Compumedics, Charlotte, NC). Acoustic startle probes were 40-ms duration, 103-dB bursts of white noise with near-instantaneous rise time presented binaurally through headphones. Electric shocks lasted 400-ms and were administered to the wrist of the participants' left hand.

Startle response was recorded from two 4-mm Ag/AgCl electrodes placed over the orbicularis oculi muscle below the right eye and the ground electrode was at the frontal pole (AFZ). Consistent with published guidelines (Blumenthal et al., 2005), one electrode was 1-cm below the pupil and the other was 1-cm lateral of that electrode. Data were collected using a bandpass filter of DC to 200 Hz at a sampling rate of 1,000 Hz. Although the upper end of this frequency band is below the Blumenthal et al. recommendation of 500 Hz, the missing bandwidth (200-500 Hz) was not likely to effect the experimental manipulation or the reliability of the results (A. Van Boxtel & T. Blumenthal, personal communication, December 14, 2009).

Startle blinks were scored according to published guidelines (Blumenthal et al., 2005). Data processing included applying a 28 Hz high-pass filter, rectifying, and then smoothing using a 40 Hz low-pass filter. Blink response was defined as the peak amplitude of electromyography (EMG) activity within the 20-150-ms period following startle probe onset relative to baseline. Each peak was identified by software but examined by hand to ensure acceptability. Blinks were scored as non-responses if EMG activity during the 20-150-ms post-stimulus timeframe did not produce a blink peak that was visually differentiated from baseline activity. Blinks were scored as missing if the baseline period was contaminated with noise, movement artifact, or if a spontaneous or voluntary blink began before minimal onset latency and thus interfered with the startle probe-elicited blink response. Descriptive analyses indicated that individual blinks were significantly skewed (range = 1.1 to 2.9) and kurtotic (range = 0.8 to 31.5) across conditions. Therefore, the amplitude of each individual blink was square-root transformed prior to analysis¹.

2.3 Data Analysis Plan

Eyeblink responses during the P_{Cue} (i.e., predictable threat) and U_{Cue} conditions (i.e., unpredictable threat) were used as the primary dependent variables. Although the U_{Cue} and U_{ISI} conditions had the same meaning (i.e., could receive a shock at any time), we chose to only examine U_{Cue} to limit comparisons and match the P and U dependent variables on visual stimuli (i.e., a geometric shape was on the screen). We also examined group differences during the N conditions to ensure that there were no baseline differences in affective reactivity or time course of affective responding.

Diagnosis was examined as two, 2-level factors, Depression Status (Present vs. Absent) and Panic Status (Present vs. Absent), instead of one 4-level factor in order to examine main effects and interactions of MDD and PD on the variables of interest.

To test whether there were group differences in the time course of aversive responding, we conducted a series of 2-level mixed growth models examining the within-individual slope of eyeblink responses across time. Mixed growth modeling is well-suited for the current aims as it allows time to be modeled continuously, accounts for the variability in durations between startle probes, and it handles missing data by weighting slope estimates by the number of observations (Goldstein, 2011). These analyses are also ideal as they model slopes within person and estimate the intercept of each individual's slope or 'initial starting point.' Time was coded as the second the startle probe occurred relative to the start of the task (onset of task = 0-secs). There were 12 consecutive startle probes presented in each condition, separated by the above mentioned break between blocks (i.e., blinks 6 and 7). Thus, there were 12 total possible blinks during P_{Cue} and U_{Cue} . The multilevel mixed model uses all startle responses as the dependent variable and estimates for each person the slope of the startle response over time and the slope intercept. Age, gender, startle task order (PNUNPU or UPNUNP), block (block 1 vs. block 2), and medication status (yes/no =

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currently taking psychiatric medications) were included as covariates in both models. Age was grand-mean centered while gender, startle task order, block, and medication status were effects coded (-0.5 or 0.5). Estimated coefficients (i.e., ' b ') are reported for multilevel mixed growth effects.

Any significant time by diagnosis (PD, MDD, or both) interaction was followed-up using a standard simple slopes approach (Aiken & West, 1991; Holmbeck, 2002). PD and/or MDD were re-coded as separate conditional moderators representing the group variable for those with and without the disorder. This approach for following up interactions is better than selecting participants in a particular group as the whole sample remains in the analyses, thus increasing statistical power.

To determine whether there were group differences in initial threat reactivity, we conducted analyses of variance (ANOVA) with each participant's estimated slope intercept output from the U_{cue} and P_{cue} multilevel mixed growth models. The use of estimated intercepts is preferable to using subjects' initial blink (i.e., blink 1 of the condition) given that the multilevel model uses all of the subjects data to estimate the intercept (i.e., beginning point of their slope) and is thus more reliable than a single blink. For our ANOVA, between subjects effects were PD, MDD, and the $PD \times MDD$ interaction. Significant interactions were followed up by conducting pair-wise comparisons between the 4 diagnostic groups (controls, MDD-only, PD-only, and comorbid).

3. Results

3.1 Clinical Characteristics

Demographic and clinical differences between the groups have been previously reported (see Shankman et al., 2013). Of note, the groups did not differ on any major demographic variable including age, gender, race, or education level. As expected, compared to controls, MDD-only individuals reported elevated current depressive symptoms (i.e., Hamilton Rating Scale of Depression scores [HRSD]; Hamilton, 1960), PD-only individuals reported elevated anxiety symptoms (i.e., Beck Anxiety Inventory scores [BAI]; Beck et al., 1988), and comorbid individuals had elevated depressive and anxiety symptoms (HRSD means $\pm$ SD: Controls= 1.7 ± 1.8 , MDD-only= 24.0 ± 7.8 , PD-only= 8.6 ± 7.2 , Comorbid= 26.5 ± 8.6 ; BAI means and standard deviations: Controls= 2.0 ± 1.9 , MDD-only= 13.7 ± 10.0 , PD-only= 15.5 ± 11.8 , Comorbid= 20.4 ± 13.3).

As previously noted, the current study included two versions of the NPU-threat task which differed in the order of condition presentation (i.e., PNUNPU or UPNUNP). Roughly half of participants in each diagnostic group got order 1 and the other half got order 2 (proportion of participants that received order 1: Controls = 44%, MDD-only = 45%, PD-only = 46%, and comorbid MDD and PD = 54%). Importantly, the groups did not differ in terms of order randomization ($\chi^2 = 2.39$, $p = 0.49$).

3.2 Initial Reactivity and Time Course of Responding During the N condition

There were no main effects of PD or MDD, or $PD \times MDD$ interactions, on initial reactivity to the N_{cue} and N_{ISI} baseline conditions (all p 's > 0.28). Time course analyses indicated that

there was a main effect of time for N_{ISI} ($b = -0.01$, $t(1342.6) = -9.94$, $p < 0.01$) and N_{Cue} ($b = -0.01$, $t(1183.5) = -10.18$, $p < 0.01$), such that the amplitude of all participants' blinks decreased over time. There were no significant main effects, 2-way, or 3-way interactions involving PD or MDD (all p 's > 0.10). Thus, groups did not differ during the baseline condition.

3.3 Initial Reactivity to Threat

For U-threat, results indicated there were no main effects of PD or MDD but there was a significant PD $\times$ MDD interaction ($F(1, 185) = 4.04$, $p < 0.05$). Individuals with MDD-only ($p = 0.04$), PD-only ($p = 0.01$), and comorbid PD-MDD ($p = 0.02$) displayed significantly greater initial startle reactivity relative to controls. However, the three diagnostic groups did not differ from each other (all p 's > 0.45 ; see Figure 1).

For P-threat, there was a main effect of PD ($F(1, 185) = 4.05$, $p < 0.05$) and a PD $\times$ MDD interaction ($F(1, 185) = 3.71$, $p = 0.05$). Individuals with PD-only ($p = 0.01$) and comorbid PD-MDD ($p = 0.03$) evidenced significantly greater startle reactivity compared with controls. MDD-only individuals evidenced greater startle reactivity relative to controls at a trend level ($p = 0.07$). The three diagnostic groups did not differ from each other (all p 's > 0.34 ; see Figure 1).

3.4 Time Course of Responding During U-Threat

Results are presented in Table 1. There was an overall significant effect of time such that the amplitude of participants' blinks decreased over time. There was no block by time interaction, but there was a main effect of block indicating that startle was greater during the first block compared with the second block. There was also a significant startle order by time interaction such that if participants received the U condition first, they exhibited a steeper slope of decline in startle responding to U-threat than individuals that received the P condition first. Consistent with prior studies (Ellwanger et al., 2003; Ludewig et al., 2003), there was a main effect of age such that as age increased, startle responding decreased. There was no significant main effect of MDD and the main effect of PD only reached trend level.

Notably, there was a significant PD by time interaction (see Figure 2A). Follow-up simple slopes analyses indicated that those with and without PD evidenced a decline in responding over time but individuals without PD ($b = -0.01$, $t(1459.7) = -6.51$, $p < 0.01$) evidenced a steeper slope than those with PD ($b = -0.01$, $t(1327.9) = -5.59$, $p < 0.01$). There was no significant MDD by time interaction or MDD by PD by time interaction.

3.5 Time Course of Responding During P-Threat

Results are presented in Table 1. Analyses indicated that there was a significant effect of time and a time by block interaction, such that the amplitude of participants' blinks decreased over time and the slope of this decrease was greater during the first block than the second block. Analogous to the U-threat model, there was also a significant startle order by time effect such that if participants received the P condition first, they exhibited a steeper slope of decline in startle responding to P-threat than individuals that received the U

condition first. There was also a main effect of age: as age increased, startle responding decreased. There was no significant main effect of MDD or PD.

There was a significant MDD by time interaction (see Figure 2B). Follow-up simple slope analyses revealed that those with and without MDD evidenced a decline in responding over time but individuals with MDD ($b = -0.01$, $t(601.6) = -10.23$, $p < 0.01$) evidenced a steeper slope than those without MDD ($b = -0.01$, $t(726.9) = -10.06$, $p < 0.01$). There was no significant PD by time or MDD by PD by time interactions.

4. Discussion

The aim of the current study was to examine group differences in reactivity to predictable and unpredictable threat, both initially and as a function of time. Results indicated that for initial threat reactivity, individuals in the three psychopathology groups (PD, MDD, and comorbid PD-MDD) evidenced greater startle reactivity to U-threat relative to controls, and did not differ from each other. A very similar pattern of results emerged for initial reactivity to P-threat, as individuals with PD and comorbid PD-MDD (and, at a trend level, MDD-only) displayed greater reactivity compared with controls (and did not differ from each other). On average, individuals evidenced the expected decline in startle over time (i.e., habituation) to P-threat and U-threat. However, most interestingly, the slope of decline varied by diagnosis and type of threat. Consistent with hypotheses, individuals with PD (with and without MDD) displayed *less of a reduction* in startle responding during U-threat relative to individuals without PD. In addition, individuals with MDD (with and without PD) displayed *greater reduction* in startle responding during P-threat compared with individuals without MDD. There are several possible explanations for this pattern of results, which will be discussed below.

4.1 Group Differences in Initial Threat Reactivity

All diagnostic groups displayed some evidence of heightened initial threat reactivity. This may be due to individual differences in threat appraisal – i.e., the tendency to overestimate the likelihood of harm and the negative consequences of such harm (Grillon, 2002; Schlotz et al., 2011; also see Clark & Beck, 2010). That is, relative to healthy controls, individuals with PD and/or MDD may perceive threat conditions as more harmful or dangerous, initiating a cascade of psychophysiological stress responses.

This explanation is consistent with extant theory and research indicating that PD is maintained by exaggerated threat appraisals of bodily sensations, such that individuals with PD perceive that innocuous interoceptive cues will result in physical, social, and mental harm (Bouton et al., 2001; Clark, 1986). It is possible that this tendency to overestimate the likelihood of harm generalizes beyond external stimuli and is a more pervasive deficit. Indeed, individuals with PD have been shown to classify stimuli as dangerous even when controls classify them as safe (e.g., Lissek et al., 2009).

Threat appraisal is often considered less relevant to the clinical picture of MDD. However, as was noted above, one study by Cuthbert et al. (2003) also found that MDD was associated with heightened initial startle reactivity, and there is a growing, broader literature suggesting

that trait-like maladaptive ways of responding to negative events is a shared vulnerability factor for depressive and anxiety disorders (Barlow, 1988; Beck, 1987; Mathews & MacLeod, 2005). In fact, a recent study demonstrated that a greater tendency to appraise naturally occurring life events as negative prospectively predicted onset of depressive and anxiety disorders five years later (Espejo et al., 2012). As such, individuals with PD and MDD (and perhaps internalizing psychopathology overall) may share a tendency to make negative *initial* appraisals, leading to heightened initial threat reactivity.

4.2 Group Differences in the Time Course of Threat Responding

Individuals with PD exhibited less of a reduction in startle responding over time during U-threat. This is consistent with earlier findings of reduced habituation to aversive stimuli in PD (Blecher et al., 2010; Roth et al., 1990). However, in our study, individuals with PD showed a *specific* deficit in habituating to unpredictable stimuli, whereas their rate of habituation to predictable stimuli was comparable to those without PD. This implies that rather than having a global emotion regulatory deficit, individuals with PD may have difficulty modulating their anticipatory anxiety to an uncertain danger but their cued fear response is relatively intact. This finding is in line with previous evidence that responding to unpredictable threat is more closely related to risk for PD than responding to predictable threat (Nelson et al., 2013).

There are several potential mechanisms that may explain these findings. For instance, responding to unpredictable threat is positively related to individual differences in sustained vigilance (Sarapas et al., 2014), and the slow rate of habituation among individuals with PD may therefore reflect a tendency to maintain a high state of threat vigilance over extended periods of time. Related to this point, as is discussed in Grupe and Nitschke (2013), individuals with anxiety disorders tend to engage in maladaptive cognitive avoidance strategies (e.g., worry) in response to uncertain threat and it is possible that these strategies maintain heightened defensive responding. Given that the current study is unable to test these different mechanisms, and the current explanations are speculative, it is important for continued work to investigate mediators that may underlie these effects.

Consistent with our hypotheses, the current findings also indicate that individuals with MDD exhibited a faster rate of habituation to P-threat compared with individuals without MDD. As was previously mentioned, studies on the association between MDD and threat responding have been extremely mixed. Some findings suggest that MDD is associated with blunted threat responding (Taylor-Clift et al., 2011; Waters et al., 2014), whereas others suggest that MDD is associated with heightened threat responding (Grillon et al., 2013; Sheline et al., 2001; Siegle et al., 2007). Meanwhile, our original analyses (Shankman et al., 2013), indicated that MDD had no impact on predictable or unpredictable threat responding. In light of the current findings, it is possible that individuals with MDD exhibit heightened initial threat reactivity but evidence a faster rate of habituation over time – particularly to P-threat. This pattern is likely lost in previous studies that averaged responses across time. Depending on the number of responses averaged, individuals with MDD could be considered to have elevated responding (as was found in Grillon et al. [2013]) or blunted

threat responding (as found in Waters et al. [2014]) and thus, assessing both forms of threat responding may be critical for future studies.

Similar to the PD time course effect, there are several potential mechanisms that may explain faster rates of habituation to predictable threats in those with MDD. As was suggested by Waters et al. (2014) and others, it is possible that individuals with MDD affectively withdraw from aversive events to a greater extent than those without MDD – particularly when the aversive events are predictable and unavoidable. Further, it is possible that after experiencing heightened initial threat responding, individuals with MDD may experience a form of “learned helplessness” whereby after their initial heightened response they become nonreactive and perceive that they have limited or no capacity to respond to impending aversive events (Dwivedi et al., 2004). In other words, in response to P-threat, individuals with MDD may disengage with the task to a greater extent than those without MDD which leads to a more rapid reduction in startle responding. As these processes are only speculative, continued research is also needed to elucidate the mechanisms underlying the time course of threat responding in MDD.

4.3 Limitations, Future Directions, and Implications

Although these findings address important gaps in the literature, there are several limitations. First, startle data was collected in two blocks separated by a 4-min rest period. Although this break was included in our time variable (i.e., time, in seconds, that the startle probe occurred including the break) and we controlled for block in our analyses, it is possible that this rest period had an effect on the present pattern of results. Therefore, future studies would benefit by examining time course continuously for a longer duration of time. Second, PD patients were allowed to meet criteria for other current and lifetime anxiety disorders and the results for PD may be for anxiety disorders in general rather than PD specifically. Third, approximately 38% of patients were taking psychiatric medications, and although we included medication status as a covariate in our analyses, it is possible that psychophysiological responding was impacted. Fourth, individuals in the depressed groups were required to have an age of onset of depression or dysthymia prior to age 18-years and it is unknown whether the current findings generalize to other subgroups of depressed individuals. Fifth, the current study included a relatively small number of comorbid MDD and PD subjects which may have limited our ability to accurately detect significant MDD by PD interactions. Future research is therefore needed to replicate the current findings and addresses these potential confounds.

Despite these limitations, there are several important implications of the current study. Results suggest that PD is characterized by heightened threat reactivity and a *slower rate* of habituation to U-threat over time relative to individuals without PD. Individuals with MDD also exhibit heightened threat reactivity but evidence a *faster rate* of habituation, specifically to P-threat relative to individuals without MDD. These results highlight the nuanced relationships between PD, MDD, and threat responding and suggest that MDD and PD may both be characterized by heightened threat reactivity but that the time course of responding is what differentiates the two disorders.

References

- Abbott B, Schoen L, Badia P. Predictable and unpredictable shock: Behavioural measures of aversion and physiological measures of stress. *Psychol. Bull.* 1984; 96:45–71. [PubMed: 6463164]
- Aiken, LS.; West, SG. Multiple regression: Testing and interpreting interactions. Sage Publications, Inc.; Thousand Oaks, CA: 1991.
- Alvarez RP, Chen G, Bodurka J, Kaplan R, Grillon C. Phasic and sustained fear in humans elicits distinct patterns of brain activity. *Neuroimage.* 2011; 1:389–400. [PubMed: 2111828]
- Banks SJ, Eddy KT, Angstadt M, Nathan PJ, Phan KL. Amygdala–frontal connectivity during emotion regulation. *Soc. Cogn. Affect. Neur.* 2007; 2(4):303–312.
- Barlow, DH. Anxiety and its disorders: The nature and treatment of anxiety and panic. Guilford; New York: 1988.
- Barlow DH. Unraveling the mysteries of anxiety and its disorders from the perspective of emotion theory. *Am. Psychol.* 2000; 55:1247–1263. [PubMed: 11280938]
- Beck AT. Cognitive models of depression. *J. Cogn. Psychother.* 1987; 1:5–37.
- Beck A, Epstein N, Brown G, Steer R. An inventory for measuring clinical anxiety: Psychometric properties. *J Consult. Clin. Psych.* 1988; 56:893–897.
- Blechert J, Wilhelm FH, Meuret AE, Wilhelm EM, Roth WT. Respiratory, autonomic, and experiential responses to repeated inhalations of 20% CO₂ enriched air in panic disorder, social phobia, and healthy controls. *Biol. Psychol.* 2010; 84(1):104–111. [PubMed: 20064582]
- Blumenthal TD, Cuthbert BN, Filion DL, Hackley S, Lipp OV, van Boxtel A. Committee report: Guidelines for human startle eyeblink electromyographic studies. *Psychophysiology.* 2005; 42:1–15. [PubMed: 15720576]
- Bouton ME, Mineka S, Barlow DH. A modern learning theory perspective on the etiology of panic disorder. *Psychol. Rev.* 2001; 108(1):4–32. [PubMed: 11212632]
- Bradley, MM.; Cuthbert, BN.; Lang, PJ. Affect and the startle reflex. In: Dawson, ME.; Schell, AM.; Bohmet, AH., editors. *Startle modification: Implication for neuroscience, cognitive science, and clinical science.* Cambridge University Press; New York: 1999. p. 157–193.
- Campbell ML, Gorka SM, McGowan SK, Nelson BD, Sarapas C, Katz AC, Robison-Andrew EJ, Shankman SA. Does anxiety sensitivity correlate with startle habituation? An examination in two independent samples. *Cognition Emotion.* 2014; 28:46–58. [PubMed: 23746071]
- Clark DM. A cognitive approach to panic. *Behav. Res. Ther.* 1986; 24(4):461–470. [PubMed: 3741311]
- Clark, DA.; Beck, AT. Cognitive therapy of anxiety disorders: Science and practice. Guilford Press; New York, NY: 2010.
- Clark, LA. The anxiety and depressive disorders: Descriptive psychopathology and differential diagnosis. In: Kendall, PC.; Watson, D., editors. *Anxiety and depression: Distinctive and overlapping features.* Academic Press; San Diego, CA: 1989. p. 83–129.
- Clark LA, Watson D. Tripartite model of anxiety and depression: Psychometric evidence and taxonomic implications. *J Abnorm. Psychol.* 1991; 100:316–336. [PubMed: 1918611]
- Cuthbert BN, Lang PJ, Strauss C, Drobos D, Patrick CJ, Bradley MM. The psychophysiology of anxiety disorder: Fear memory imagery. *Psychophysiology.* 2003; 40:407–422. [PubMed: 12946114]
- Davidson RJ. Affective style and affective disorders: Perspectives from affective neuroscience. *Cognition Emotion.* 1998; 12:307–330.
- Davis M. Are different parts of the extended amygdala involved in fear versus anxiety? *Biol. Psychiat.* 1998; 44:1239–1247. [PubMed: 9861467]
- Davis M. Neural systems involved in fear and anxiety measured with fear-potentiated startle. *Am. Psychol.* 2006; 61:741–56. [PubMed: 17115806]
- Davis M, Walker DL, Miles L, Grillon C. Phasic vs sustained fear in rats and humans: Role of the extended amygdala in fear vs anxiety. *Neuropsychopharmacology.* 2010; 35(1):105–135. [PubMed: 19693004]

- Dwivedi Y, Mondal AC, Shukla PK, Rizavi HS, Lyons J. Altered protein kinase A in brain of learned helpless rats: Effects of acute and repeated stress. *Biol Psychiatry*. 2004; 56:30–40. [PubMed: 15219470]
- Ellwanger J, Geyer MA, Braff DL. The relationship of age to prepulse inhibition and habituation of the acoustic startle response. *Biol. Psychol.* 2003; 62(3):175–195. [PubMed: 12633977]
- Espejo EP, Hammen C, Brennan PA. Elevated appraisals of the negative impact of naturally occurring life events: A risk factor for depressive and anxiety disorders. *J. Abnorm. Child Psychol.* 2012; 40(2):303–315. [PubMed: 21845380]
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for DSM–IV Axis I Disorders, Clinician Version (SCID-CV). American Psychiatric Press; Washington, DC: 1996.
- Goldstein, H. Multilevel statistical models. Vol. 922. John Wiley & Sons; 2011.
- Gorka SM, McGowan SK, Campbell ML, Nelson BD, Sarapas C, Bishop JR, Shankman SA. Association between respiratory sinus arrhythmia and reductions in startle responding in three independent samples. *Biol Psychol.* 2013; 93:334–341. [PubMed: 23528785]
- Gorka SM, Nelson BD, Shankman SA. Startle response to unpredictable threat in comorbid panic disorder and alcohol dependence. *Drug Alcohol Depend.* 2013; 132(1):216–222. [PubMed: 23465734]
- Gorman JM, Kent J, Martinez J, Browne S, Coplan J, Papp LA. Physiological changes during carbon dioxide inhalation in patients with panic disorder, major depression, and premenstrual dysphoric disorder: Evidence for a central fear mechanism. *Arch. Gen. Psychiat.* 2001; 58:125–131. [PubMed: 11177114]
- Grillon C. Startle reactivity and anxiety disorders: Aversive conditioning, context, and neurobiology. *Biol. Psychiat.* 2002; 52(10):958–975. [PubMed: 12437937]
- Grillon C, Baas JP, Lissek S, Smith K, Milstein J. Anxious responses to predictable and unpredictable aversive events. *Behav. Neurosci.* 2004; 118:916–924. [PubMed: 15506874]
- Grillon C, Baas JMP, Pine DS, Lissek S, Lawley M, Ellis V, Levine J. The benzodiazepine alprazolam dissociates contextual fear from cued fear in humans as assessed by fear-potentiated startle. *Biol. Psychiat.* 2006; 60:760–766. [PubMed: 16631127]
- Grillon C, Franco-Chaves JA, Mateus CF, Ionescu DF, Zarate CA. Major depression is not associated with blunting of aversive responses; Evidence for enhanced anxious anticipation. *PloS One.* 2013; 8(8):e70969. [PubMed: 23951057]
- Grillon C, Lissek S, Rabin S, McDowell D, Dvir S, Pine DS. Increased anxiety during anticipation of unpredictable but not predictable aversive stimuli as a psychophysiological marker of panic disorder. *Am. J. Psychiat.* 2008; 165(7):898–904. [PubMed: 18347001]
- Gross JJ. Emotion regulation: Past, present, future. *Cognition Emotion.* 1999; 13(5):551–573.
- Groves PM, Thompson RF. Habituation: A dual-process theory. *Psychol. Rev.* 1970; 77:419–450. [PubMed: 4319167]
- Grupe DW, Nitschke B. Uncertainty and anticipation in anxiety: an integrated neurobiological and psychological perspective. *Nat. Rev. Neurosci.* 2013; 14(7):488–501. [PubMed: 23783199]
- Hamilton M. A rating scale for depression. *J. Neurol. Neurosurg. Ps.* 1960; 23:56–62.
- Harris JD. Habituation response decrement in the intact organism. *Psychol. Bull.* 1943; 40(6):385.
- Heller W, Nitschke JB. The puzzle of regional brain activity in depression and anxiety: The importance of subtypes and comorbidity. *Cognition Emotion.* 1998; 12:421–447.
- Herry C, Ferraguti F, Singewald N, Letzkus JJ, Ehrlich I, Luthi A. Neuronal circuits of fear extinction. *Eur. J. Neurosci.* 2010; 31:599–612. [PubMed: 20384807]
- Holmbeck GN. Post-hoc probing of significant moderational and mediational effects in studies of pediatric populations. *J. Pediatr. Psychol.* 2002; 27(1):87–96. [PubMed: 11726683]
- Kendler KS, Prescott CA, Myers J, Neale MC. The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. *Arch. Gen. Psychiat.* 2003; 60:929–937. [PubMed: 12963675]
- Kessler RC, Crum RM, Warner LA, Nelson CB, Schulenberg J, Anthony JC. Lifetime co-occurrence of DSM-III-R alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Survey. *Arch. Gen. Psychiat.* 1997; 54:313–321. [PubMed: 9107147]

- Kessler RC, Demler O, Frank RG, Olfson M, Pincus HA, Walters EE, Wang P, Wells KB, Zaslavsky AM. Prevalence and treatment of mental disorders, 1990 to 2003. *New Engl. J. Med.* 2005; 352(24):2515–2523. [PubMed: 15958807]
- Kessler RC, Nelson CB, McGonagle KA, Lui J, Swartz M, Blazer DG. Comorbidity of DSM-III-R major depressive disorder in the general population: Results from the National Comorbidity Survey. *Brit. J. Psychiat.* 1996; 168:17–30.
- Lang PJ. The emotion probe: Studies of motivation and attention. *Am. Psychol.* 1995; 50:372–385. [PubMed: 7762889]
- Lissek S, Rabin SJ, McDowell DJ, Dvir S, Bradford DE, Geraci M, Pine DS, Grillon C. Impaired discriminative fear-conditioning resulting from elevated fear responding to learned safety cues among individuals with panic disorder. *Behav. Res. Ther.* 2009; 47(2):111–118. [PubMed: 19027893]
- Ludewig K, Ludewig S, Seitz A, Obrist M, Geyer MA, Vollenweider FX. The acoustic startle reflex and its modulation: effects of age and gender in humans. *Biol. Psychol.* 2003; 63(3):311–323. [PubMed: 12853174]
- Mathews A, MacLeod C. Cognitive vulnerability to emotional disorders. *Ann. Rev. Clin. Psychol.* 2005; 1:167–195. [PubMed: 17716086]
- Melzig CA, Weiike AI, Zimmermann J, Hamm AO. Startle reflex modulation and autonomic responding during anxious apprehension in panic disorder patients. *Psychophysiology.* 2007; 44:846–854. [PubMed: 17640268]
- Mineka S, Watson D, Clark LA. Comorbidity of anxiety and unipolar mood disorders. *Ann. Rev. Psychol.* 1998; 49:377–412. [PubMed: 9496627]
- Mogg K, Bradley B, Miles F, Dixon R. Time course of attentional bias for threat scenes: Testing the vigilance-avoidance hypothesis. *Cognition Emotion.* 2004; 18(5):689–700.
- Nelson BD, McGowan SK, Sarapas C, Robison-Andrew EJ, Altman SE, Campbell ML, Gorka, Katz AC, Shankman SA. Biomarkers of threat and reward sensitivity demonstrate unique associations with risk for psychopathology. *J. Abnorm. Psychol.* 2013; 112:662–671. [PubMed: 24016008]
- Oken BS, Salinsky MC, Elsas SM. Vigilance, alertness, or sustained attention: Physiological basis and measurement. *Clin Neurophysiol.* 2006; 117:1885–1901. [PubMed: 16581292]
- Oldfield RC. The assessment and analysis of handedness: The Edinburgh Inventory. *Neuropsychologia.* 1971; 9:97–113. [PubMed: 5146491]
- Phan KL, Fitzgerald DA, Nathan PJ, Moore GJ, Uehde TW, Tancer ME. Neural substrates for voluntary suppression of negative affect: A functional magnetic resonance imaging study. *Biol. Psychiat.* 2005; 57(3):210–219. [PubMed: 15691521]
- Rankin C, Abrams T, Barry R, Bhatnagar S, Clayton D, Colombo J, Coppola G, Geyer MA, Glanzman DL, Marsland S, McSweeney FK, Wilson DA, Wu CF, Thompson RF. Habituation revisited: An updated and revised description of the behavioral characteristics of habituation. *Neurobiol. Learn. Mem.* 2009; 92(2):135–138. [PubMed: 18854219]
- Rollman GB, Harris G. The detectability, discriminability, and perceived magnitude of painful electrical shock. *Percept. Psychophys.* 1987; 42:257–268. [PubMed: 3671051]
- Roth WT, Ehlers A, Taylor CB, Margraf J, Agras WS. Skin conductance habituation in panic disorder patients. *Biol. Psychiat.* 1990; 27(11):1231–1243. [PubMed: 2191728]
- Sarapas C, Langenecker SA, Shankman SA. Relationships among components of attention and defensive responding. 2014 Manuscript under editorial review.
- Schlotz W, Hammerfeld K, Ehlert U, Gaab J. Individual differences in the cortisol response to stress in young healthy men: Testing the roles of perceived stress reactivity and threat appraisal using multiphase latent growth curve modeling. *Biol. Psychol.* 2011; 87(2):257–264. [PubMed: 21419825]
- Schmitz A, Grillon C. Assessing fear and anxiety in humans using the threat of predictable and unpredictable aversive events (the NPU-threat test). *Nat. Protoc.* 2012; 7:527–532. [PubMed: 22362158]
- Shankman SA, Gorka SM, Nelson BD, Fitzgerald DA, Phan L, O'Daly O. Anterior insula responds to temporally unpredictable aversiveness: an fMRI study. *Neuroreport.* 2014; 25:596–600. [PubMed: 24614364]

- Shankman SA, Klein DN. The relation between depression and anxiety: An evaluation of the tripartite, approach-withdrawal and valence-arousal models. *Clin. Psychol. Rev.* 2003; 23:605–637. [PubMed: 12788112]
- Shankman SA, Nelson BD, Sarapas C, Robison-Andrew EJ, Campbell ML, Altman SE, McGowan SK, Katz AC, Gorka SM. A psychophysiological investigation of threat and reward sensitivity in individuals with panic disorder and/or major depressive disorder. *J. Abnorm. Psychol.* 2013; 122:322–328. [PubMed: 23148783]
- Sheline YI, Barch DM, Donnelly JM, Ollinger JM, Snyder AZ, Mintun MA. Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: An fMRI study. *Biol. Psychiat.* 2001; 50:651–658. [PubMed: 11704071]
- Siegle GJ, Thompson W, Carter CS, Steinhauer SR, Thase ME. Increased amygdala and decreased dorsolateral prefrontal BOLD responses in unipolar depression: Related and independent Features. *Biol. Psychiat.* 2007; 61:198–209. [PubMed: 17027931]
- Taiminen T, Jääskeläinen S, Ilonen T, Meyer H, Karlsson H, Lauerma H, Leinonen KM, Wallenius E, Kaljonen A, Salokangas RK. Habituation of the blink reflex in first-episode schizophrenia, psychotic depression and non-psychotic depression. *Schizophr. Res.* 2000; 44(1):69–79. [PubMed: 10867313]
- Taylor-Clift A, Morris BH, Rottenberg J, Kovacs M. Emotion-modulated startle in anxiety disorders is blunted by co-morbid depressive episodes. *Psychol Med.* 2011; 41(01):129–139. [PubMed: 20230657]
- Vollebergh WAM, Iedema J, Bijl RV, de Graaf R, Smit F, Ormel J. The structure and stability of common mental disorders: The NEMESIS study. *Arch. Gen. Psychiat.* 2001; 58:597–603. [PubMed: 11386990]
- Waters AM, Nazarian M, Mineka S, Zinbarg RE, Griffith JW, Naliboff B, Ornitz E, Craske MG. Context and explicit threat cue modulation of the startle reflex: Preliminary evidence of distinctions between adolescents with principal fear disorders versus distress disorders. *Psychiat Res.* 2014; 217(1):93–99.
- Watson D. Differentiating the mood and anxiety disorders: A quadripartite model. *Ann. Rev. Clin. Psychol.* 2009; 5:221–247. [PubMed: 19327030]
- Werner, K.; Gross, JJ. Emotion regulation and psychopathology: A conceptual framework. In: Kring, A.; Sloan, D., editors. *Emotion regulation and psychopathology: A transdiagnostic approach to etiology and treatment.* Guilford Press; New York: 2010. p. 13-37.

Highlights

- Panic disorder and depression are associated with high initial threat reactivity.
- Panic disorder is associated with slower habituation to unpredictable threat.
- Depression is associated with faster habituation to predictable threat.

Fig. 1. Mean slope intercept/initial startle reactivity to predictable and unpredictable threat across diagnostic groups. Startle amplitude is square-root transformed.

Fig. 2.

A) The effect of PD on startle amplitude across time during unpredictable threat; B) The effect of MDD on startle amplitude across time during predictable threat; PD = panic disorder; MDD = major depressive disorder; Startle amplitude is square-root transformed.

Table 1
Mixed growth models examining group differences in the time course of threat responding

Variable	U-Threat			P-Threat		
	<i>b</i>	<i>t</i>	<i>p</i> -value	<i>b</i>	<i>t</i>	<i>p</i> -value
Block 1						
Intercept	1.90	1.88	0.06	4.50*	4.51	<0.01
Time	<0.01*	-7.40	<0.01	-0.01*	-15.14	<0.01
Age	-0.04*	-2.18	0.03	-0.04*	-2.48	0.01
Gender	0.08	0.33	0.74	-0.02	-0.09	0.93
Block	1.96*	8.45	<0.01	2.11*	12.26	<0.01
Task Order	0.76	1.72	0.09	-0.36	-0.80	0.42
Medication	0.97	1.70	0.09	0.88	1.52	0.13
PD	0.70	1.46	0.15	0.75	1.56	0.12
MDD	<0.01	-0.01	0.99	-0.20	-0.41	0.68
Block 2						
Intercept	5.99*	4.70	<0.01	7.92*	9.05	<0.01
Age × Time	<0.01	1.18	0.24	<0.01	-0.17	0.87
Gender × Time	<0.01	0.46	0.64	<0.01	-1.44	0.15
Block × Time	<0.01	-0.85	0.40	<0.01*	3.39	<0.01
Task Order × Time	<0.01*	12.83	<0.01	<0.01*	7.73	<0.01
Medication × Time	<0.01	-0.59	0.56	<0.01	0.60	0.55
PD × Time	<0.01*	2.15	0.03	<0.01	1.19	0.24
MDD × Time	<0.01	-0.78	0.47	<0.01*	-2.20	0.03
Block 3						
Intercept	5.98*	4.79	<0.01	7.78*	6.95	<0.01
PD × MDD × Time	<0.01	0.59	0.55	<0.01	-0.34	0.73

Note.

* indicates $p < 0.05$; PD = panic disorder; MDD = major depressive disorder.