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Cognitive Flexibility Mediates the Relation between Intolerance of Uncertainty and Safety Signal Responding in those with Panic Disorder

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Abstract

There is a growing literature associating anxiety disorders with an inability to inhibit defensive responding during safety conditions of threatening tasks. However, investigations on the relation between panic disorder (PD) and defensive responding to safety have yielded mixed results. A recent study from our laboratory revealed that intolerance of uncertainty (IU) moderates this association, such that only individuals with PD and high IU exhibit heightened startle potentiation during safety. The mechanism underlying this relationship is unknown. Given that safety conditions typically alternate with periods of threat, cognitive flexibility (i.e., the ability to adjust one's habitual responding to a situation, given the input of new information) may be involved in the ongoing reappraisal of danger and adjustment of defensive responding. Thus, the present study sought to investigate whether deficits in cognitive flexibility mediate the association between IU and defensive responding to safety among a sample of 71 adults diagnosed with PD. As hypothesized, cognitive flexibility mediated the relationship between IU and heightened startle potentiation during safety conditions. This finding suggests that within this subgroup, a failure to inhibit defensive responding during safety conditions may be due to deficits in cognitive flexibility.

Keywords

Panic disorder; Intolerance of uncertainty; Cognitive flexibility; Safety signals; Defensive responding

A wealth of previous research indicates that anxiety disorders are associated with heightened defensive responding to threat (Grillon et al., 2008; Shankman et al., 2013). More recently, some have suggested that an inability to inhibit defensive responding during safety signals is another core dysfunction related to anxiety disorders (Davis et al., 2000). Consistent with this, individuals with anxiety disorders such as social phobia (Hermann, Ziegler, Birbaumer & Flor, 2002), posttraumatic stress disorder (Grillon & Morgan, 1999), and panic disorder (PD; Lissek et al., 2009) have been shown to exhibit greater defensive responding during safety signals relative to healthy controls. Moreover, defensive responding to safety in

adolescents has been found to longitudinally predict the development of anxiety disorders in adulthood (Craske et al., 2012), suggesting that this aberrant emotional response may contribute to the pathogenesis of anxiety disorders.

However, some investigations have failed to find a relation between anxiety and defensive responding to safety (e.g., Michael, Blechert, Vriends, Margraf & Wilhelm, 2007), indicating that certain individual differences factors may influence this association. Indeed, our laboratory recently found that intolerance of uncertainty (IU) – the trait-like tendency to appraise unpredictable events as distressing or threatening (Carleton, Fetzner, Hackl & McEvoy, 2013) – moderates the association between PD and heightened defensive responding to safety (Gorka, Lieberman, Nelson, Sarapas & Shankman, 2014). Specifically, we found that individuals with PD showed heightened responding during safety conditions of a threatening task only if they also had high levels of IU (Gorka et al., 2014). Of note, IU is an important trait among individuals with PD as it is associated with the situational avoidance symptoms of the disorder (even over and above traits like anxiety sensitivity; Carleton et al., 2013).

The propensity to exhibit defensive responding in the presence of safety may represent an important treatment target for this subgroup, especially given the salience of this abnormality for PD. Individuals with PD have been found to experience fear in response to harmless (i.e., “safe”) bodily sensations (Rapee, Ancis & Barlow, 1988). Although the factors underlying the association between IU and defensive responding to safety among those with PD is currently unknown, further study is warranted as it may identify key treatment targets for this emotional deficit.

Cognitive flexibility – the ability to adjust one’s emotional, cognitive, and behavioral responding to a situation based on new information (Johnco, Wuthrich & Rapee, 2014; Martin & Rubin, 1995) – is one factor that may explain why IU results in heightened defensive responding during safety signals among those with PD. First, IU appears to be associated with poorer cognitive flexibility. For example, high-IU individuals tend to categorically appraise uncertainty and ambiguity as negative or threatening (Dugas et al., 2005), and are likely to engage in perseverative forms of thinking such as worry (Dugas, Gosselin & Ladouceur, 2001). In turn, defensive responding in the presence of a safety condition can be conceptualized as a failure of cognitive flexibility – i.e., a failure to redirect one’s cognitions away from past or future threat. To apply this conceptualization specifically to panic disorder, individuals with panic disorder may demonstrate heightened anxiety in safe contexts due to difficulty shifting their attention away from memories of past panic attacks and/or from apprehension concerning future attacks. Consistent with this idea, cognitive (in)flexibility is closely linked to rumination (i.e., failure to shift thoughts away from past threat; Davis & Nolen-Hoeksema, 2000; Joorman, Levens & Gotlib, 2011) and worry (i.e., failure to shift thoughts away from future threat; Lee & Orsillo, 2014). More generally, cognitively inflexible individuals have greater difficulty filtering out task-irrelevant threatening information (Stout, Shackman, Johnson, Larson, 2014) and demonstrate resistance to altering cognition or behavior based on new information (Hamtiax & Houssemand, 2012; Steinmetz, Loarer & Houssemand, 2011).

The present study therefore sought to extend our previous finding of IU's association with defensive responding to safety (Gorka et al., 2014) by conducting a reanalysis of the Gorka et al. (2014) dataset. More specifically, we examined whether cognitive flexibility (a variable which was not reported in Gorka et al. [2014]) mediates the association between IU and defensive responding to safety among individuals with PD. Defensive responding to safety conditions was assessed during a well-validated threat-of-shock startle paradigm, the No Shock-Predictable Threat-Unpredictable Threat task (i.e., NPU-threat task, Schmitz & Grillon, 2012). The NPU task presents individuals with varying, frequently shifting levels of threat – no shock (N), predictable shock (participants can only be shocked when a warning cue is present [P_{cue}], and are safe when the cue is absent [P_{ISI}]), and unpredictable shock (U – shocks can be delivered at any time). Virtually every study employing this task has reported a significant task effect (e.g., Shankman et al., 2013; Grillon et al., 2013), indicating that individuals shift their affective responding in response to these shifting contingencies. Thus, the NPU threat task is capable of eliciting shifts in defensive responding between its various conditions, and of capturing individual differences in these shifts.

Consistent with Gorka et al. (2014), startle responding during the P_{ISI} condition was used as the measure of defensive responding to safety. This was done because P_{ISI} is a brief safety condition that is interleaved with threat conditions (i.e., P_{cue}). Given the brevity of P_{ISI} and its proximity to the onset of threat, this condition may best be characterized as a *weak situation*, or a situation in which the degree to which an individual is safe is somewhat ambiguous, and thus more susceptible to eliciting individual differences in defensive reactivity (Lissek, Pine & Grillon, 2006). Moreover, the interleaving of acute threat (i.e., P_{cue}) with periods of safety (i.e., P_{ISI}) is analogous to the experience of individuals with PD, in which panic-attack-free periods are punctuated by periods of acute fear (i.e., panic attacks). Defensive responding during P_{ISI} is thus akin to the “Criterion B” anxiety and apprehension that individuals with PD often demonstrate between panic attacks.

Thus, we tested using data from Gorka et al. (2014), the hypothesis that among those with PD, the association between IU and defensive responding to safety would be mediated by individual differences in cognitive flexibility. To test the specificity of this effect, we also examined whether cognitive flexibility mediates the association of IU with defensive responding to threat (and not just safety). It is also important to add that heightened IU has been implicated in the development of generalized anxiety disorder, social anxiety disorder, and obsessive-compulsive disorder, (Boelen & Reijntjes, 2009). Therefore, investigating the underlying mechanisms of the association between IU and defensive responding to safety among those with PD could prove valuable to the understanding of defensive responding to safety in other anxiety disorders.

Methods

Participants

The current sample included 71 individuals with a current diagnosis of PD who were recruited as part of a larger investigation on affective processes that included 74 individuals with PD (Shankman et al., 2013)¹. The current sample of individuals with PD was the same

as the Gorka et al. (2014) sample, and thus the present study was a reanalysis of data from Gorka et al. (2014). Although all 74 individuals with PD from the Shankman et al. (2013) sample were included in the Gorka et al. (2014) sample, three were excluded from the present study because they did not complete neuropsychological testing. Participants were 50.7% Caucasian, 14.1% Latino, 8.5% Asian, and 19.7% African American; 64.8% female; and had an average age of 34.55 years ($SD = 11.88$). All diagnoses were made using the Structured Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 1996). Individuals were excluded from participation if they had a lifetime history of psychosis, bipolar disorder, dementia, or head trauma with loss of consciousness, or were left-handed. Individuals were also excluded if they were unable to read or write in English. All participants provided informed consent.

Procedure and NPU-Threat Task

As mentioned above, defensive responding to safety conditions was assessed during a well-validated threat-of-shock startle paradigm, the NPU-threat task (Schmitz & Grillon, 2012). Throughout the task, text was presented at bottom of the screen which read, “No shock” (N), “Shock possible during square” (P), or “Shock at any time” (U), to remind participants of the current condition. During each 90-s condition, a different geometric cue (blue circle during N, red square during P, and green star during U) was presented for 8-s. Inter-stimulus intervals (ISIs) ranging from 7 to 17-s ($M = 11.6$ -s) occurred in between cue presentations, during which only text indicating the current condition remained on screen. Of note, the mean ISI duration was equivalent across blocks of the task. No shocks were delivered during N, shocks were only delivered when the cue was present during P, and shocks were delivered at any time (i.e., during the cue or ISIs) during U.

The task occurred in two blocks that were separated by a 5-minute break. Each condition, consisting of four cue presentations, occurred twice within each block. Conditions were presented in the following counterbalanced orders: PNUNPU or UPNUNP. Subjects viewed a fixation cross in between each condition for 5 seconds. Defensive responding was indexed by potentiation of the eyeblink startle reflex. Responding during the P_{ISI} condition was used as the measure of defensive responding to safety.

Participants received 6 shocks during P and 6 during U. There were 24 startle probes delivered in each condition (for a total of 72). Twelve startle probes were presented during the cues (i.e., N_{Cue} , P_{Cue} , and P_{ISI}), 2–7 s following the cue onset, and 12 during the ISIs (i.e., N_{ISI} , P_{ISI} , U_{ISI}), 4–12 s following ISI onset. No more than one startle probe was delivered during each presentation of the cue or each ISI. Startle probes never followed shocks by fewer than 10-s, so that startle responding was unaffected by a preceding shock. Shocks during P_{Cue} were always presented at either the 6th or 7th second of the 8-second cue, whereas shocks during the U cue were presented at random. Startle probes never followed shocks by fewer than 10-s, so that startle responding was unaffected by a preceding shock. Prior to the threat task, participants listened to 9 acoustic startle probes over the course of 2.5-minutes so as to habituate early startle responding. To select an ideographically appropriate shock level to be used throughout the task, participants completed a shock work-up procedure for which shocks of increasing intensity were

administered until a level was reached that the participant described as “highly annoying, but not painful” (Grillon & Schmitz, 2012). The maximum shock level a participant could achieve was 5 mA, and the mean shock level selected was 2.2 mA ($SD = 1.3$).

Startle Data Collection and Processing

All stimuli were delivered using PSYLAB (Contact Precision Instruments, London, UK). Acoustic startle probes were 103-dB bursts of 40-ms white noise with near instantaneous rise time, presented binaurally through headphones. Electric shocks 400-ms in duration were administered to participants' left wrist.

Physiological data was collected using Neuroscan 4.4 (Compumedics, Charlotte, NC). 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-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 and T. Blumenthal, personal communications, December 14, 2009).

Startle blinks were scored according to published guidelines (Blumenthal et al., 2005). Data were first rectified and then smoothed using a FIR filter with a band pass of 28–40 Hz. Blink response was defined as the peak amplitude of electromyogram (EMG) activity within the 20- to 150-ms period following startle probe onset relative to baseline (average baseline EMG level for the 50 ms preceding the startle probe onset). Each peak was identified by software but was examined by hand to ensure acceptability (e.g., not a double blink). Blinks were scored as nonresponses if EMG activity during the 20- to 150-ms poststimulus timeframe did not produce a blink peak that was visually differentiated from baseline activity. Blinks were scored as missing (i.e., excluded) 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. Analyses were conducted using blink amplitude (i.e., condition averages do not include non-responses). We chose to use amplitude in the present study so as to remain consistent with the manuscript on which the present study was based on (i.e., Gorka et al., 2014, in which we found IU to moderate the association between PD and defensive responding during P_{ISI}). However, the below pattern of results was identical when blink magnitudes were used (i.e., condition averaged that include 0's for non-responses).

Cognitive Flexibility

Cognitive flexibility was assessed using the Verbal and Design Fluency subtests of the widely used Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan & Kramer, 2001) neuropsychological battery. Verbal Fluency included three conditions: Letter Fluency, Category Fluency, and Category Switching. For Letter Fluency, participants were to list as many words as possible that begin with the letters *F*, *A*, and *S*, with 60 seconds allotted per

letter. For Category Fluency, participants were to list as many *boy's names* and *animals* as possible, with 60 seconds allotted per category. Total scores for Letter and Category Fluency conditions were calculated as the number of non-repeating, appropriate words generated within the time limit. The Category Switching condition, which indexes cognitive flexibility, requires participants to switch back and forth between listing as many *fruits* and *pieces of furniture* as possible within 60 seconds. A Category Switching score was calculated as the total number of successful switches made within the time limit.

Similar to the Verbal Fluency subtests, Design Fluency consisted of three conditions: Basic, Filter, and Switch. In the Basic Condition, participants were presented with 35 squares that each contained the same array of five black dots. Participants were given 60 seconds to create a different design in each square using only four straight lines to connect the dots, ensuring that each line meets at least one other line at a dot. During the Filter Condition, each of the 35 squares presented were filled with five empty dots and five black dots. Participants were given 60 seconds to create a different design in each square to connect only the empty dots, while following the same rules from the previous condition. Finally, during the Switch condition, each of the 35 squares was again filled with five empty and five black dots. Subjects were given 60 seconds to create a different design in each square by switching between an empty and a filled dot to create each line. For each condition, a total score was calculated as the number of unique and appropriate designs generated within the time limit.

Performance on the Category Switching condition of Verbal Fluency and Design Switching condition of Design Fluency was used to index cognitive flexibility (Kalkut, Han, Lansing, Holdnack & Delis, 2009). Both Verbal and Design Fluency have comparably strong reliabilities and overall psychometric properties (Shunk, Davis & Dean, 2006) and correlate with other measures of cognitive flexibility (e.g., the stroop Ross et al., 2007).

Intolerance of Uncertainty

Participants completed the Intolerance of Uncertainty Scale (IUS; Freeston, Rhéaume, Letarte, Dugas & Ladouceur, 1994), a 27-item questionnaire assessing the trait-like belief that uncertainty is unacceptable, reflects poorly on a person, and leads to frustration, stress, and the inability to take action. Responses are rated on a five-point Likert scale ranging from 1 (not at all characteristic of me) to 5 (entirely characteristic of me), with higher scores indicating greater intolerance of uncertainty. Prior factor analyses on the 27-item IUS have found a 12-item version with better psychometric properties (Carleton et al., 2013). Thus, the present study used the total score of the 12-item version of the IUS scale. Reliability of 12-item IUS total scores was excellent ($\alpha = .96$).

Data Analysis Plan

Analyses to test mediation were conducted using a nonparametric bootstrapping method, in line with recommendations by MacKinnon et al. (2004). Models were tested using the SPSS macro PROCESS (Hayes, 2012), which calculates a bootstrap estimate of the indirect effect between the independent variable and dependent variable, an estimated standard error, and 95% confidence intervals (CI) for the population value of the indirect effect. Analyses were

conducted using 1000 bootstrap samples. Prior to conducting analyses, scores on the Category Switching and Design Switching categories were averaged together, and all variables were z-scored to produce standardized β weights.

We first tested our hypothesis that cognitive flexibility mediates the association between IU and defensive responding to safety among individuals with PDAs explained above, consistent with Gorka et al. (2014), mean startle potentiation during the P_{ISI} condition was used as the primary dependent variable. Potentiation scores account for individual differences in baseline startle responding by subtracting startle amplitude during the control condition (i.e., $P_{ISI} - N_{ISI}$). Mean startle responding during the P_{ISI} condition was z-transformed after potentiation scores were calculated. The following formula was used to z-transform startle potentiation during the P_{ISI} condition:

$$z = \frac{(P_{ISI} - N_{ISI}) - \mu_{(P_{ISI} - N_{ISI})}}{\sigma_{(P_{ISI} - N_{ISI})}}$$

IU was specified as the independent variable and cognitive flexibility as the mediator. Cognitive flexibility was measured as a composite score of performance on the Category Switching and Design Switching conditions. Finally, depression status (yes/no) and gender were specified as covariates.

Once our hypothesis was confirmed, we ran several additional models to test the specificity of the effect. First, we replaced cognitive flexibility with a composite measure of cognitive fluency (i.e., performance on the Letter/Category [Verbal] and Basic/Filter [Design] conditions) as the mediator between intolerance of uncertainty and safety signal responding. The purpose of this analysis was to rule out the possibility that fluency more broadly, rather than cognitive flexibility in particular, accounted for the mediation effect. Second, we replaced startle potentiation to safety signals with startle potentiation to explicit threat (i.e., $P_{Cue} - N_{ISI}$, $U_{Cue} - N_{ISI}$, and $P_{ISI} - N_{ISI}$) as the dependent variable, and tested whether cognitive flexibility also mediated the relation between intolerance of uncertainty and threat responding. The rationale for these models was to confirm that our findings were specific to safety responding, rather than being related to startle responding more broadly.

Results

Mediating Effect of Cognitive Flexibility

Results indicated that greater IU was predictive of less cognitive flexibility, $\beta = -.25$, $t(70) = -2.10$, $p < .05$, and in turn, less cognitive flexibility was predictive of greater P_{ISI} startle potentiation, $\beta = -.36$, $t(70) = -3.10$, $p < .01$. There was no effect of IU on P_{ISI} startle potentiation, $\beta = .20$, $t(70) = 1.64$, *ns*, but there was a significant indirect effect of IU on P_{ISI} startle potentiation, mediated through cognitive flexibility, $\beta = .09$, 95% CI [.00, .25] (see Figure 1a). Of note, there was no effect of depression on P_{ISI} startle potentiation, $\beta = -.23$, $t(70) = -.97$, *ns*. The aforementioned effects remained when depression was removed from the model (indirect effect, $\beta = .09$, 95% CI [.01, .24]

Given the cross-sectional nature of the mediation, we tested the significance of a mediation model when cognitive flexibility was the independent variable and IU was the mediator. This model yielded no significant indirect effect of cognitive flexibility on P_{ISI} through IU, $\beta = -.03$, 95% CI: $[-.12, .02]$. Finally, to test the specificity of the effects to safety, we tested whether cognitive flexibility mediated the association of IU and defensive responding during threat conditions. None of these models yielded significant indirect effects: U_{ISI} , $\beta = .05$, 95% CI $[-.01, .20]$, U_{Cue} , $\beta = .01$, 95% CI $[-.06, .13]$, or P_{Cue} , $\beta = .02$, 95% CI $[-.03, .16]$.

Alternative Mediational Models: Fluency

To examine whether the effects were specific to cognitive flexibility rather than to the ability to generate responses quickly (i.e., fluency), a mediation model was run with fluency as the mediator. Results indicated that IU was not predictive of fluency, $\beta = 0.05$, $t(70) = 0.42$, *ns*, and fluency was not predictive of P_{ISI} startle potentiation, $\beta = -0.08$, $t(70) = -0.70$, *ns*. Moreover, there was no significant indirect effect of IU on P_{ISI} startle potentiation, mediated through fluency, $\beta = -.00$, 95% CI $[-0.05, 0.01]$ (see Figure 1b).

Discussion

It has been suggested that individuals with anxiety disorders fail to inhibit defensive responding in the presence of safety information in the environment, and that this might play a role in the etiology and maintenance of anxiety disorders (Craske et al., 2012; Lissek et al., 2009). Consistent with this, anxiety disorders have been associated with heightened defensive responding during safety signals of threatening tasks (Grillon & Morgan, 1999; Hermann, Ziegler, Birbaumer & Flor, 2002). However, recent findings from our laboratory suggest that IU may moderate the association between anxiety disorders and defensive responding to safety, such that only those with high IU exhibit this pattern (Gorka et al., 2014). Given the growing literature indicating the role of high IU in the development and maintenance of PD and other anxiety disorders (Boelen & Reijntjes, 2009; Carleton, et al., 2013), the present study sought to investigate a potential mediator of the relationship between IU and defensive responding to safety among those with PD. Results suggest that deficits in cognitive flexibility underlie the association between IU and defensive responding to safety among those with PD. Moreover, this relationship was *not* mediated by measures of fluency that did not require cognitive flexibility, which indicates that cognitive inflexibility *specifically* underlies this association, rather than a broader deficit in fluency.

Cognitive inflexibility has been associated with difficulty in adjusting cognitions, attitudes and behaviors, given the input of new information (Hamtiaux & Houssemad, 2012; Steinmetz et al., 2011). Therefore, the present findings may suggest that PD individuals high in IU have appraised the *entirety* of the P condition as threatening and failed to adjust that appraisal during the safety part of the condition (P_{ISI}). Therefore, this subgroup may continue to display defensive responding during safety due to rigidity in their assessment of the situation as threatening. It is noteworthy that this mediation was specific to defensive responding during the safety but not threat conditions responding as only the former requires shifting response sets.

Alternatively, our results may indicate that PD individuals with high IU and low cognitive flexibility have particular difficulty disengaging from worry about future threat or rumination about past threat during safety conditions. A large literature has linked IU to worry and GAD (Dugas et al., 2001; Freeston et al. 1994). As mentioned above, poor cognitive flexibility is also associated with worry (Lee & Orsillo, 2014) and rumination (Davis & Nolen-Hoeksema, 2000; Joorman, Levens & Gotlib, 2011). Thus, due to deficits in cognitive flexibility, PD individuals with high IU may have difficulty switching their attentional focus from cognitions about past or future threat to the present safe situation, resulting in a failure to down-regulate defensive responding during safety conditions.

The present findings may contribute to our understanding of the mechanisms underlying the development and maintenance of PD. If individuals with PD and high IU had difficulty disengaging from threat in the presence of safety during NPU, this deficit may contribute to the progression from a benign bodily sensation to a full-blown panic attack. For example, if an individual of this subgroup experiences a symptom of anxiety, they may appraise that sensation as dangerous. Cognitive inflexibility could prevent reinterpretation of the situation, despite evidence of safety (e.g., a heart palpitation that ends immediately). Likewise, if this subgroup of individuals appraised the entirety of the NPU task (or perhaps just the P condition) as threatening, this may suggest a tendency to categorically appraise situations as threatening even in the presence of safety. Thus, this subgroup of individuals may categorically appraise all physiological symptoms of anxiety as threatening.

Although IU had significant indirect effects on defensive responding to safety mediated by cognitive flexibility, we did not find a significant *direct* effect of IU on defensive responding. This is consistent with current theory on mediation, which holds that mediational effects may exist even in the absence of a significant direct effect (Hayes, 2009). One possible explanation for this is that a competing, unmeasured mediator exercised effects opposite to those of the cognitive flexibility, in effect “canceling out” the direct effect of IU. Alternatively, the direct effect may be so small that it was not detected in this sample, whereas the indirect effect was of greater magnitude.

Several limitations should be noted in interpreting this study. First, we relied on set-shifting tasks to examine cognitive flexibility. Although set-shifting is often considered the core of cognitive flexibility (Martin & Rubin, 1995), some models posit that cognitive flexibility has other components such as divided attention (Peterson, Smith & Carson, 2002). Future studies should therefore assess the association of other indicators of cognitive flexibility with IU and defensive responding. Second, although we found that simple verbal and design fluency did not mediate effects of IU on defensive responding, we did not assess other aspects of executive function (e.g., inhibition or attentional control). Third, different geometric shapes and colors may differentially influence defensive responding. Geometric shape and color were confounded within the NPU blocks, and thus may have influenced startle potentiation (Larson, Aronoff, Sarinopoulos, & Zhu, 2009). Fourth, there has not been rigorous research to explore the construct validity of affective responding during the inter-stimulus intervals of NPU. Thus, future research on affective responding during these conditions is warranted. Finally, participants were permitted to be on medication, which may have influenced physiological indices of defensive responding. Of note, when medication

status was controlled for, the indirect effect of cognitive flexibility on defensive responding to safety remained significant. The current study also had several strengths, including indexing cognitive flexibility with multiple measures and assessing defensive responding via startle.

In sum, the present study highlights cognitive inflexibility as a potential target for future treatment research among those with PD and high IU. Given that IU has been implicated across multiple anxiety disorders (Boelen & Reijntjes, 2009), future investigation of the role of cognitive flexibility in defensive responding to safety in other anxiety disorders is also warranted.

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Figure 1a.

Figure 1b.

Figure 1.

Figure 1a. The mediating effect of cognitive flexibility

Figure 1b. The mediating effect of fluency

¹Although self-ratings of anxiety/nervousness were also obtained from participants (Gorka et al., 2014; Shankman et al., 2013), we chose not to include these measures in the present manuscript because IU did not moderate the association between PD and subjective ratings of anxiety/nervousness. Therefore, we could not examine a mediator of this association.