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# Aversive startle potentiation and fear pathology: Mediating role of threat sensitivity and moderating impact of depression

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## ABSTRACT

Enhanced startle reactivity during exposure to unpleasant cues (aversive startle potentiation; ASP) appears in the RDoC matrix as a physiological index of acute threat response. Increased ASP has been linked to focal fear disorders and to scale measures of dispositional fearfulness (i.e., threat sensitivity; THT+). However, some studies have reported *reduced* ASP for fear pathology accompanied by major depressive disorder (MDD) or pervasive distress. The current study evaluated whether (a) THT+ as indexed by reported dispositional fearfulness mediates the relationship between fear disorders (when unaccompanied by depression) and ASP, and (b) depression moderates relations of THT+ and fear disorders with ASP. Fear disorder participants without MDD showed *enhanced* ASP whereas those with MDD (or other distress conditions) showed evidence of *reduced* ASP. Continuous THT+ scores also predicted ASP, and this association: (a) was likewise moderated by depression/distress, and (b) accounted for the relationship between ASP and fear pathology without MDD. These findings point to a role for the RDoC construct of acute threat, operationalized dispositionally, in enhanced ASP shown by individuals with fear pathology unaccompanied by distress pathology.

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## 1. Introduction

The National Institute of Mental Health's Research Domain Criteria (RDoC) initiative calls for progress toward alternative neurobiologically informed conceptions of psychiatric disorders (Sanislow et al., 2010). The initiative encourages the investigation of core biobehavioral constructs with relevance to multiple clinical problems across differing levels of analysis, from genetic and neuro-cellular to brain systems/processes to domains of observable behavior and perceived experience. However, empirical examples demonstrating how constructs specified in the RDoC framework can serve as bridges between neurophysiology and clinical problems are needed. The current study addresses this need by demonstrating a role for dispositional threat sensitivity (THT+; the trait counterpart to acute threat sensitivity in RDoC) as indexed by scores on a self-report dimension of fear/fearlessness (Kramer, Patrick, Krueger, and Gasperi, 2012) in mediating the relationship between fear disorders and aversive startle potentiation (ASP), a physiological index of activation of the brain's defensive system. Extending prior research, the current work also demonstrates a moderating impact of major depression on associations of fear pathology and threat sensitivity with ASP—suggesting that the co-occurrence of depression with fear symptomatology may signify the presence of a distinct pathophysiological condition (Rosen and Schulkin, 1998; Lang and McTeague, 2009).

## 1.1. Aversive startle potentiation: associations with fear disorders and dispositional threat sensitivity

Excessive emotional responding to discrete stimuli perceived as harmful or threatening is a core feature of focal fear disorders such as specific and social phobia, agoraphobia, and panic disorder. Negative emotional reactivity to such discrete aversive cues, reflecting the activation of the brain's core defensive system, can be measured in terms of enhancement (potentiation) of the noise-elicited blink-startle reflex (Bradley, Codispoti, Cuthbert, and Lang, 2001; Lang, 1995)—and individuals high in reported fearfulness show increased startle reflex potentiation during viewing or imagery of aversive compared to neutral scenes (Cook et al., 1991; Cook, Davis, Hawk, Spence, and Gautier, 1992; Vaidyanathan, Patrick, and Bernat, 2009a; see also Lissek and Powers, 2003). Similarly, individuals with specific phobias show measurably greater startle potentiation than controls when viewing or imaging scenes related to their phobias (Hamm, Cuthbert, Globisch, and Vaitl, 1997; Globisch, Hamm, Esteves, and Ohman, 1999). Enhanced startle potentiation during fear-relevant cuing (i.e., increased ASP) has also been reported in individuals diagnosed with social phobia, particularly of the circumscribed (performance-related) type (Lang, McTeague, and Cuthbert, 2007; McTeague et al., 2009). Findings for panic disorder have been more mixed. Cuthbert et al. (2003) reported that panic disorder patients (relative to healthy controls and other anxiety patients) showed diminished rather than enhanced ASP during imagery of personalized fear scenes, while showing a trend toward enhanced *general reactivity* as indexed by startle magnitude during non-imagery

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(intertrial) intervals. Somewhat in contrast with this, Lang et al. (2007) found ASP during personal aversive imagery to be reduced in panic patients relative to phobic patients, but greater for panic patients than for GAD patients or controls.<sup>1</sup>

Regarding the role of threat sensitivity in fear pathology, it has been hypothesized that high dispositional reactivity of the brain's core defensive system, encompassing the amygdala and affiliated structures, constitutes a liability factor for focal fear disorders (Rosen and Schulkin, 1998). In RDoC terms, the dispositional liability for disorders of this type corresponds to the construct of "acute threat" in the "Negative Valence Systems" domain. Importantly, a quantitative-structural model exists for measures of reported fear versus fearlessness in relation to specific objects/situations, social contexts, danger/uncertainty, and other stressful circumstances (Kramer et al., 2012). The model, formulated using data from a large adult twin sample, specifies a broad common factor on which all scale measures load substantially; this factor can be viewed as reflecting individual differences along a dimension of dispositional threat sensitivity (THT+). Consistent with this perspective, scores on this factor predict degree of ASP (i.e., compared to intermediate scorers, individuals with low scores on this factor showed reduced ASP, and those with high scores show enhanced ASP; Kramer et al., 2012; Vaidyanathan et al., 2009a). Additionally, scores on the THT+ factor are appreciably heritable (Kramer et al., 2012)—as would be expected of an underlying liability factor. In sum, existing research has demonstrated associations for focal fear disorders and reported fearful tendencies with ASP in different cuing contexts, including picture viewing. Based on the idea of dispositional threat sensitivity (THT+) as a liability for fear-related disorders, the current study evaluated the possibility that individual differences in this dispositional variable (operationalized as scores on the common factor shown to underlie various scale measures of situational fear/fearlessness) might account for the relationship between fear disorder diagnoses and ASP.

## 1.2. Moderating impact of depression on fear/startle associations

Data from a number of studies have produced evidence that the presence of major depression, or perhaps distress pathology more broadly, moderates the relationship between fear pathology and ASP. In work examining startle modulation during imaginal processing of fear-relevant and neutral scenarios, Lang et al. (2007) found that patients with focal fear disorders showed greater ASP than patients with diffuse anxiety conditions, and that patients of either type with co-morbid depression showed reduced startle potentiation compared to those without co-morbid depression. Additionally, these investigators reported that diffuse-anxiety patients with comorbid depression displayed the greatest levels of pervasive distress (negative affectivity) as indexed by multiple self-report measures. Subsequent work by Taylor-Clift, Morris, Rottenberg, and Kovacs (2011) evaluated the moderating impact of comorbid depression on the relationship between anxiety conditions and emotion modulated startle in a picture viewing paradigm. These investigators found that healthy controls and individuals with current anxiety disorders unaccompanied by depression exhibited robust startle potentiation during aversive scenes (relative to neutral), whereas individuals with anxiety disorders and co-morbid depression failed to show such potentiation. Similar to this, a more recent study by Vaidyanathan, Welo, Malone, Burwell, and Iacono (2014) found that subjects with recurrent depression (relative to

single-episode or never-depressed subjects) exhibited a flattened affect-startle pattern, providing further evidence that depression exerts a suppressive effect on startle modulation.

In sum, available evidence indicates that the expected increase in ASP during aversive picture viewing or image processing in individuals with anxiety disorders, and focal fear conditions in particular, may be moderated by the presence of co-morbid depression—which operates to dampen startle potentiation. Extending beyond findings for depression, work by Lang and colleagues (e.g., Lang et al., 2007; Lang and McTeague, 2009; McTeague, Lang, Wangelin, Laplante, and Bradley, 2012) suggests that it may be pervasive distress and dysphoria more broadly, rather than depression per se, that accounts for this suppressive effect on ASP. The current study was conducted to further address questions pertaining to affective individual differences, internalizing psychopathology, and startle reactivity.

## 1.3. Current study hypotheses

Building on prior published work as described, the current study tested the following specific hypotheses:

- (1) Fear disorder participants will show increased ASP relative to non-fear-disorder participants, but only in the absence of a history of major depression, or (per work by Lang et al.) distress conditions more broadly;
- (2) ASP will covary positively with dispositional threat sensitivity (THT+) as indexed by scores on a self-report based measure of variations in fear/fearlessness;
- (3) THT+ will mediate the observed relationship between ASP and fear disorder diagnosis (when not accompanied by major depressive disorder [MDD] or other distress pathology).

## 2. Materials and methods

### 2.1. Participants

The base sample for the study consisted of 508 adult twins (257 female) recruited from the greater Twin Cities metro area who participated for a payment of \$100. Most participants were tested concurrently with their co-twin (of the same gender, in all cases, by design), within the same scheduled session but by different experimenters in separate lab rooms. Participants were selected for testing based on levels of THT+ (see the next section), and were free of visual or hearing impairments as assessed by a screening questionnaire. From among the full base sample, 55 participants were excluded from analyses due to unstable/noisy blink EMG signals or excessive zero-amplitude trials (see the "Data reduction" section), and 32 were excluded due to missing physiological or self-report data. Data for the remaining participants with valid blink startle data and relevant questionnaire/diagnostic information ( $N = 421$ ; 222 female, 199 male) were utilized in the analyses describe below.

### 2.2. Dispositional and diagnostic measures

#### 2.2.1. Dispositional threat sensitivity (THT+): Trait Fear inventory

Participants were assessed for levels of THT+ using an inventory developed to index a broad dimension of fear/fearlessness identified through structural modeling analyses (Kramer et al., 2012; see also Vaidyanathan et al., 2009a; Vizueta, Patrick, Jiang, Thomas, and He, 2012). The inventory consists of 55 items drawn from various established self-report inventories of fear and fearlessness, including the Fear Survey Schedule-III (Arrindell et al., 1984), the Fearfulness subscale of the EAS Temperament Survey (Buss and Plomin, 1984), the Harm Avoidance subscale of the Temperament and Personality Questionnaire (Cloninger, 1987), subscales comprising Factor 1 of the Psychopathic Personality Inventory (Lilienfeld and Andrews, 1996),

<sup>1</sup> Notably, studies utilizing threat of shock as opposed to aversive pictures or imagery have also reported somewhat mixed findings for panic disorder. For example, Grillon et al. (2008) reported enhanced startle potentiation in an unpredictable aversive condition (uncued delivery of shock) among patients with panic disorder selected to be depression-free, and Melzig et al. (2007) similarly found that panic patients without comorbid depression showed enhanced ASP under conditions of shock-threat, whereas those with comorbid depression did not. By contrast, Nelson et al. (2013) reported enhanced ASP during shock-threat in individuals with a family history of panic disorder, regardless of history of comorbid depression.

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