Archival Report

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Distinct Responses to Predictable and Unpredictable Threat in Anxiety Pathologies: Effect of Panic Attack

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ABSTRACT

BACKGROUND: Delineating specific clinical phenotypes of anxiety disorders is a crucial step toward better classification and understanding of these conditions. The present study sought to identify differential aversive responses to predictable and unpredictable threat of shock in healthy comparisons and in nonmedicated anxiety patients with and without a history of panic attacks (PAs).

METHODS: In this study, 143 adults (72 healthy control subjects; 71 patients with generalized, social, or both generalized and social anxiety disorders, 24 with and 47 without PAs) were exposed to three conditions: 1) predictable shocks signaled by a cue, 2) unpredictable shocks, and 3) no shock. Startle magnitude was used to assess aversive responses.

RESULTS: Across disorders, a history of PAs was specifically associated with hypersensitivity to unpredictable threat. By disorder, social anxiety disorder was associated with hypersensitivity to predictable threat, whereas generalized anxiety disorder was associated with exaggerated baseline startle.

CONCLUSIONS: These results identified three physiological patterns. The first is hypersensitivity to unpredictable threat in individuals with PAs. The second is hypersensitivity to predictable threat, which characterizes social anxiety disorder. The third is enhanced baseline startle in generalized anxiety disorder, which may reflect propensity for self-generated anxious thoughts in the absence of imminent danger. These results inform current thinking by linking specific clinical features to particular physiology profiles.

Keywords: Anxiety, Anxiety disorder, Fear, Panic attack, Predictability, Startle

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Research on pathophysiology and biomarkers informs the search for new treatments for anxiety disorders (1–3). Pathological anxiety can be conceptualized as excessive fear or anxiety in response to threat (4), which manifest in various ways at both the behavioral and neural levels (5). Therefore, the physiological correlates of fear and anxiety may be particularly useful biomarkers. The present study compares physiologic responding to predictable and unpredictable threat in individuals with generalized anxiety disorder (GAD), social anxiety disorder (SAD), panic attacks (PAs), or no mental disorder.

The startle reflex indexes heterogeneous features of aversive states as they manifest across species. Particularly consistent results arise in research on predictable and unpredictable threats, which evoke aversive responses with overlapping but distinct neural origins. Specifically, while an imminent and predictable threat induces a phasic fear response mediated by the amygdala, an unpredictable threat induces a more sustained anxiety state mediated by the bed nucleus of the stria terminalis (BNST) (5). This distinction between fear, a response to "acute threat," and anxiety, a response to "potential harm," is reflected in the Research Domain Criteria (3).

In a translational extension of this approach, we developed a protocol to examine responses to predictable and unpredictable shock in humans (6,7). In the so-called neutral, predictable, and unpredictable (NPU) threat test paradigm, fear and anxiety are operationally defined as the increase in startle magnitude from a neutral condition to a period of predictable (i.e., fear-potentiated startle) and unpredictable (i.e., anxiety-potentiated startle) shock anticipation, respectively.

In separate studies, we used the NPU test to examine physiologic responses in various clinical conditions. We reported a selective hypersensitivity to unpredictable but not predictable threat in panic disorder (PD) and posttraumatic stress disorder (PTSD) (8,9) and normal responses to predictable and unpredictable threats in GAD (9). This latter result was contrary to the expectation that GAD would be associated with exaggerated response to an unpredictable threat, given that core GAD symptoms include sustained anticipatory anxiety and uncontrollable worry (10–12).

A potential explanation for these negative results in GAD is that we used mild aversive stimuli (i.e., air blasts directed to the neck, loud unpleasant sounds) rather than shocks, which are more unpleasant and evoke robust anxiety-potentiated startle (6). To investigate this possibility, the current study used shock. It was expected that individuals with GAD would be hypersensitive to unpredictable shocks.

Little is currently known about aversive responses during shock anticipation in SAD. Individuals with SAD show exaggerated startle potentiation to social threat (13,14) but not to commonly shared threat (e.g., physical attack by animal or human) (13). However, to the best of our knowledge, no study has yet been published on startle reactivity during shock anticipation in SAD. Neuroimaging studies point to hyperactivity, especially in the amygdala, in response to discrete (i.e., predictable) emotional stimuli, including nonsocial stimuli, in SAD (15,16). Based on these observations, we hypothesized that SAD would be associated with a hypersensitivity to a predictable threat.

PAs consist of abrupt, overwhelming fear and terror. Although PAs are the hallmark of PD, they are also among the most common symptoms in anxiety disorders and other psychiatric disorders (17). In fact, PAs constitute a nonspecific risk factor for psychopathology (17), which has led to their inclusion as a specifier in DSM-5 (4). Therefore, a better understanding of PAs could have far-reaching implications for our comprehension of psychiatric conditions.

As aforementioned, we have reported hypersensitivity to unpredictable threat in PD (8). Similarly, another group, also relying on the NPU threat test, has reported that hypersensitivity to unpredictable threat, but not predictable threat, was associated with increased familial liability for PD (18). Given that PAs define PD, these results raise the possibility of an association between PAs and unpredictable threat rather than predictable threat (5,19). In fact, we have obtained preliminary evidence for such an association in an ongoing family study of mood and anxiety disorders (20). The present study, therefore, tested the hypothesis that PAs are associated with hypersensitivity to unpredictable threat by comparing individuals with GAD, SAD, or both, with and without a history of PAs.

To summarize, the present work sought to identify potential clinical phenotypes by examining the pattern of responses to predictable and unpredictable threats in individuals with GAD, SAD, or both, with or without a history of PAs. We hypothesized that compared with control subjects, a history of PAs or a diagnosis of GAD would be associated with enhanced anxiety-potentiated startle to unpredictable threat, but with normal fear-potentiated startle to predictable threat. Finally, we hypothesized that SAD would be associated with normal anxiety-potentiated startle, but enhanced fear-potentiated startle, reflecting a hypersensitivity to predictable threat.

METHODS AND MATERIALS

Participants

A total of 71 medication-free patients with an anxiety disorder (51 women) and 74 healthy control subjects (51 women) participated in the study. Participants were recruited from the Washington, DC, metropolitan area through flyers, e-mail lists, and newspaper advertisements. There were three lines of recruitment: 1) for "anxiety and worry problems" aimed at recruiting individuals with an anxiety disorder, 2) individuals who had experienced panic attacks, and 3) for healthy control subjects. Following an initial telephone screen, participants visited the National Institutes of Health for comprehensive screening by a psychologist and a physician or a nurse practitioner. The patients had a diagnosis of GAD ($n = 27$) or SAD ($n = 21$) or had comorbid GAD and SAD ($n = 24$). All patients with SAD (except one in the combined GAD and SAD group) had generalized social anxiety disorder. No other current Axis I psychiatric disorder, or past psychosis as assessed by the Structured Clinical Interview for DSM-IV Axis I disorders (21) were allowed. A total of 45 patients had never been medicated with anxiolytics and of the 26 who had taken anxiolytics, only 8 took medication in the past 1 to 6 months. All patients were free of medication for at least 3 weeks prior to testing. Healthy comparisons had no current or past Axis I psychiatric diagnosis according to the Structured Clinical Interview for DSM-IV. A subsample of the anxious patients ($n = 24$) reported having experienced unexpected PAs (18 reported at least two and six reported at least one) (Table 1). PAs were symptoms of intense fear as described in DSM-IV. Two comparison subjects reported at least two PAs. However, due to their small numbers, the two comparisons with PAs were excluded, though analyses including or excluding these subjects generated similar conclusions, as presented in Supplemental Table S1. Mean age (Table 1) did not significantly differ across groups ($t_{142} = 0.40$, not significant [ns]). All subjects were free of illicit substances, as per urine screen. None of the subjects had participated in a NPU threat test before. Written informed consent was obtained after detailed description of the study.

Procedure

On the day of the physical and psychiatric screen, participants filled out the trait portion of the State-Trait Anxiety Inventory (22). Prior to the NPU threat test, participants completed the state portion of the State-Trait Anxiety Inventory, the Beck Depression Inventory (BDI) (23), the Beck Anxiety Inventory (24), the Penn State Worry Questionnaire (25), and then were fitted with two electrodes under their left eye to record the electromyographic eyeblink/startle reflex. To assess baseline startle, participants were exposed to nine acoustic startle stimuli every 18 to 23 seconds via headphones (habituation startle). A shock work-up was also implemented to set the intensity of shock to a mildly painful level.

The NPU threat procedure is shown in Supplemental Figure S1. It is described in detail in Schmitz and Grillon (7) and was similar to that used in our previous clinical and psychopharmacological studies (9,26). Participants were given explicit instructions regarding the threat test, which consisted of three 150-second conditions: 1) no threat (N), 2) predictable threat (P), and 3) unpredictable threat (U). In each 150-second condition, an 8-second duration cue was presented four times. The cues differed in color and shape for each condition (e.g., blue square for N, red circle for P, green triangle for U). The cues signaled the possibility of receiving a shock in the