Anxious Responses to Predictable and Unpredictable Aversive Events

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Anxiety induced by 2 types of predictable and unpredictable aversive stimuli, an unpleasant shock or a less aversive airblast to the larynx, were investigated in a between-group design. Participants anticipated predictable (signaled) or unpredictable (not signaled) aversive events, or no aversive event. Unpredictable, relative to predictable, contexts potentiated the startle reflex in the shock group but not in the airblast group. These data suggest that unpredictability can lead to a sustained level of anxiety only when the pending stimulus is sufficiently aversive. Because predictable and unpredictable danger may induce different types of aversive responses, the proposed design can serve as a useful tool for studying the neurobiology and psychopharmacology of fear and anxiety.

In both humans and animals, two types of aversive states can be identified following the administration of aversive stimuli (e.g., electric shocks) signaled by a cue: a phasic fear response to the threat cue (explicit cue fear) and a more sustained anxiety state to the experimental context (contextual fear; see Davis, 1998). There is now substantial evidence to suggest that patients with anxiety disorders are abnormally sensitive to contextual fear, which increases baseline startle (see Grillon, 2002a, 2002b). For example, during experiments in which shocks were signaled by a threat cue, Vietnam veterans with posttraumatic stress disorder (PTSD) showed exaggerated startle responses throughout the testing procedure, including the periods when subjects were not at risk of receiving a shock (absence of the threat cue), compared to non-PTSD controls (Grillon, Morgan, Davis, & Southwick, 1998). This group difference in baseline startle disappears if testing takes place in an innocuous context where no shock is expected. Similar findings have been reported in patients with panic disorder (Grillon, Ameli, Goddard, Woods, & Davis, 1994), in Desert Storm veterans with PTSD (Grillon & Morgan, 1999), in urban police officers with PTSD (Pole et al., 2003), and in individuals at high risk for anxiety disorders (Grillon, Dierker, & Merikangas, 1998) or major depression (Grillon, Hille, Warner, & Weissman, 2003). Despite this elevation in baseline startle, we have not found that startle during the threat cue (fear-potentiated startle) is increased in anxious patients (Grillon et al., 1994; Grillon, Morgan, et al., 1998). These results are particularly interesting because they suggest that sustained contextual anxiety, but not phasic explicit cue

fear, differentiates anxious from nonanxious individuals (Grillon, Morgan, et al., 1998; Pole, Neylan, Best, Orr, & Marmar, 2003).

Because contextual fear may help identify a general affective abnormality in anxious patients and in individuals at high risk for anxiety, procedures need to be designed to study contextual fear and to identify conditions that affect (e.g., increase) this emotional state. Such procedures may help improve understanding of the neurobiology of aversive motivation as well as the underlying psychopathology of anxious patients.

Contextual Fear and Predictability

Currently, little is known about contextual fear in humans, but data from animal studies suggest that predictability is a major determinant of contextual fear. Evidence from the Pavlovian conditioning literature indicates that fear elicited by an aversive stimulus varies as a function of the probability that the aversive stimulus is signaled by a cue (Rescorla & Wagner, 1972). Indeed, signaled (predictable) shocks produced less context conditioning than nonsignaled (unpredictable) shocks in animals (A. G. Baker, Mercier, Gabel, & Baker, 1981; Bouton, 1984; Fanselow, 1980; Marlin, 1981; Odling-Smee, 1975). Similar results have been reported in humans (Grillon & Davis, 1997). Grillon and Davis studied context conditioning in two groups of subjects returning to an experimental room where they had previously received fear conditioning with either unpredictable or predictable shock (unpaired light–shock and paired light–shock, respectively). Results showed that context conditioning was greater when the shocks were unpredictable compared to when they were predictable.

The *safety-signal hypothesis* (Seligman & Binik, 1977) provides a rationale for these findings. According to the safety-signal hypothesis, when an organism can predict threat because it is signaled by a cue, the absence of the threat signal comes to predict the absence of danger, that is, safety. However, when aversive events are not signaled (unpredictable), the periods of safety are also not signaled. In the absence of periods of safety, the organism remains in a state of chronic anxiety and sustained anxious anticipation. From this, it follows that in an experimental condition in which aversive events are predicted by a cue, the absence of that cue will

lead to less anxiety than a condition in which the aversive events cannot be predicted.

Because unpredictable aversive events are particularly effective for inducing contextual anxiety, and because contextual anxiety differentiates individuals with and without anxiety disorders, experimental paradigms eliciting anxious reactivity to unpredictability may provide useful tools for probing psychophysiological correlates of pathological anxiety.

Experimental and Theoretical Approaches to Unpredictability

Studies of unpredictability have focused on the overall impact of predictable and unpredictable aversive stimuli on behavior, psychological well-being, and health. Animal studies have provided substantial empirical evidence demonstrating that animals prefer predictability over unpredictability and that predictable danger is less debilitating than unpredictable danger (Mineka, Cook, & Miller, 1984; Mineka & Kihlstrom, 1978; Overmier & Wielkewicz, 1983), although negative results have also been reported (Arthur, 1986; Tsuda & Hirai, 1976).

At a theoretical level, predictability has long been postulated to be fundamental to anxiety and anxiety disorders (Foa, Zinbarg, & Rothbaum, 1992). Animal research has suggested that unpredictable aversive stimuli cause debilitating cognitive, behavioral, and somatic effects similar to those found in clinical anxiety and mood disorders (Maier, 1991; Mineka & Kihlstrom, 1978). These effects can be prevented when the aversive event is made predictable (Mineka et al., 1984; Mineka & Kihlstrom, 1978). Predictability is a key feature of several anxiety disorders, including PTSD (Foa et al., 1992) and panic disorder (Craske, Glover, & DeCola, 1995). For example, the unpredictable nature of panic attacks contributes to the general worry about recurring panic attacks and the high level of chronic, anxious apprehension that characterizes individuals with this condition (Craske et al., 1995).

Empirical studies in humans have yielded inconsistent results as to whether unpredictable aversive events are more anxiogenic than predictable aversive events. Although humans seem to prefer predictability to unpredictability (Abbott & Badia, 1979; Lejuez, Eifert, Zvolensky, & Richards, 2000; Pervin, 1963), it has been difficult to find consistent differences in physiological arousal between predictable and unpredictable conditions. Geer and Maisel (1972) reported increased electrodermal reactivity associated with unpredictability. However, a review of experimental studies conducted before the 1980s concluded that predictable danger caused more physiological (and subjective) arousal than unpredictable danger (see Miller, 1979). Results from recent investigations continue to be inconclusive as to the effects of predictability on physiological arousal, with several studies reporting no difference between predictable or unpredictable aversive stimuli (CO_2, loud noise, disturbing pictures; Lejuez et al., 2000; Taylor, Carlson, Iacono, Lykken, & McGue, 1999; Vogeltanz & Hecker, 1999).

There are several possible explanations for these contradictory findings in humans. For example, some investigators have evaluated physiological responding during the anticipatory period, whereas others have focused on the actual impact of the aversive stimulus. The present study focused on the anticipation of aversive events that varied by degree of temporal predictability. Other factors that may also have contributed to contradictory results include the type of physiological assessment of anxiety and the nature of the aversive stimulus. These two factors are discussed below.

Physiological Responses to Threat

Research on fear and anxiety has been hampered by problems of measurement. Traditional psychophysiological autonomic measures of aversive states, such as heart rate (HR) and the various measures of electrodermal activity (skin conductance responses [SCRs], nonspecific skin conductance response [NS-SCR], skin conductance level [SCL]), are nonspecific indices of arousal, and therefore indirect measures of anxiety. Failure to detect differences in physiological reactions to predictable and unpredictable aversive events may reflect limitations in the sensitivity of these measures to changes in anxiety.

The startle reflex has emerged as a valid investigative tool for measuring emotional responses to aversive stimuli (for reviews, see Davis, Falls, Campeau, & Kim, 1993; Grillon & Baas, 2003). The startle reflex is potentiated by fear and anxiety in humans and animals (Davis & Astrachan, 1978; Grillon, Ameli, Woods, Merikangas, & Davis, 1991), making it a useful measure for translational research. In particular, the fear-potentiated startle effect has been linked to activation of distinct neural structures involved in phasic fear responses to explicit threat cues and in sustained aversive responses to context, namely, the amygdala and the bed nucleus of the stria terminalis, respectively (Davis, 1998). In addition, startle has been shown to be sensitive to aversive states elicited by both signaled and nonsignaled shocks in humans in fear conditioning experiments (Grillon & Davis, 1997; Grillon & Morgan, 1999), suggesting that this measure may help better distinguish between the effects of predictable and unpredictable danger, compared to more traditional psychophysiological measures.

Shock Versus Airblast

In the present study, we were especially interested in comparing the effect of predictability on emotional reactions to shocks and a class of stimulation that is by nature less noxious: airblasts. On one hand, predictability could be preferred over unpredictability for its own sake, because the ability to predict events in the environment is important for the comfort of organisms (Staub, Tursky, Schwartz, 1971). In other words, uncertainty and unpredictability could be intrinsically aversive. Alternatively, unpredictability could be a significant aspect of emotional reactivity to danger only for certain types of stimuli that are sufficiently noxious or unpleasant (Mineka & Kihlstrom, 1978). This is an important empirical question because various types of unpleasant stimuli are used to study aversive states, including shocks, pictures, CO_2, or loud sounds, and less noxious stimuli are preferred to minimize impact on subjects, especially those from vulnerable populations such as children and patients. For this purpose, we have introduced unpleasant blasts of air (airblast) to the larynx as an alternative to shocks (Grillon & Ameli, 1998), a technique that is being used increasingly (McManis, Smidman, & Kagan, 1999; Monk et al., 2003; Verona, Patrick, & Lang, 2002). Previous studies have

documented substantial startle potentiation during the anticipation of predictable shocks (Grillon et al., 1991) and airblasts (Grillon & Ameli, 1998). In this study, we seek to establish whether both types of stimuli induce contextual fear as mediated by unpredictability.

To summarize, the present study investigated emotional responses to predictable and unpredictable aversive stimuli. The following two main questions were investigated. Do unpredictable aversive events produce more fear or anxiety as assessed physiologically than predictable events, and is the effect of unpredictability affected by the aversive nature of the aversive stimulus (shock or airblast)?

Method

Participants

Participants were 72 healthy volunteers, equally divided into a shock group (20 men, 16 women) and an airblast group (19 men, 17 women), with equivalent mean age and average scores on trait measures of anxiety and depression (Table 1, see below for description). Participants gave written informed consent that had been approved by the National Institute of Mental Health Human Investigation Review Board. Inclusion criteria included (a) no past or current psychiatric disorders as per Structured Clinical Interview for *DSM-IV* (SCID: First, Spitzer, Williams, & Gibbon, 1995), (b) no medical condition that interfered with the objectives of the study, and (c) no use of drugs or psychoactive medications as per self-report.

Procedure

Participants underwent a screening session that consisted of a SCID; a physical exam; and either a shock workup procedure (shock group) to establish a level of shock that was "highly annoying but not painful," or the delivery of two airblasts directed at the level of the larynx (airblast group). Participants were also asked to fill out the Spielberger's State and Trait Anxiety Inventory (Spielberger, 1983); the Beck Depression Inventory (Beck & Steer, 1987); and the Penn State Worry Questionnaire (Meyer, Miller, Metzger, & Borkovec, 1990), a 16-item questionnaire designed to assess the tendency to worry.

Four to 10 days later, participants returned for a testing session. This session started with a 10-min rest period that terminated with a 2-min recording of baseline physiological activity (except startle). This was followed by the presentation of nine startle stimuli delivered every 18–25 s to assess the baseline startle reflex prior to the threat study. Participants were then given explicit instructions regarding the conditions under which they would and would not receive an aversive event. After the instructions, the threat experiment began.

The experiment consisted of three different conditions: predictable shock (P), unpredictable shock (U), and no aversive stimulus (N), each lasting 2 min. In the N condition, no aversive stimuli (shock or airblast) were delivered. In the P condition, aversive stimuli were administered predictably, that is, only in the presence of a threat cue. In the U condition, aversive stimuli were unpredictable (see below). In each 2-min condition, an 8-s duration cue was presented twice. The cues were geometric colored shapes in the different conditions (e.g., blue circle for N and green square for P). The cues signaled the possibility of receiving an aversive stimulus only in the P condition, but they had no signal value in the N and U conditions. A computer monitor informed participants of the current condition by displaying the following information: "no shock" or "no blast" (N), "shock (or blast) only during shape" (P), or "shock (or blast) at any time" (U). This information was present for the duration of each N, P, and U condition. During each predictable and unpredictable condition, two aversive stimuli (shocks or blasts) were administered. The stimuli were administered at cue offset in the predictable condition and in the absence of the cues in the unpredictable condition. Acoustic startle stimuli were delivered (a) 5–6 s following the onset of each cue and (b) during intertrial intervals (ITIs; i.e., between cues) every 20–40 s. The time interval between a shock or airblast and the following startle probes was the same in the predictable and unpredictable conditions. The experiment was designed so that there was a 30-s stimulus-free period in each condition that was used to examine tonic physiological activity (as opposed to phasic changes caused by the cues).

The threat experiment consisted of two recording blocks with a 5–10-min rest between blocks. Each block consisted of three N, two P, and two U conditions in one of the following two orders: P N U N U N P or U N P N P N U. Each participant was presented with the two orders, with half the participants starting with the P condition.

Stimuli, Physiological Responses, and Psychometric Assessments

Stimulation and recording were controlled by a commercial system (Contact Precision Instruments, Cambridge, MA). The physiological measures included eyeblink electromyograph (startle reflex), skin conductance, HR, and finger pulse volume (FPV). The acoustic startle stimulus was a 40-ms duration, 103 dB(A) burst of white noise with a near instantaneous rise time, presented binaurally through headphones. The eyeblink reflex was recorded with electrodes placed under the left eye. Amplifier bandwidth was set to 30–500 Hz. The left palmar skin conductance was recorded from the index and middle finger of the left hand according to published recommendations (Prokasy & Ebel, 1967). The HR was monitored with two electrodes placed on each side of the chest. Left FPV was recorded with a photoplethysmograph.

The electric shock was produced by a constant current stimulator and administered on the right wrist. It had a duration of 100 ms, and its intensity ranged from 3–5 μA (mean = 4.2 μA). The airblast was an

Table 1
Mean Participant Age, Anxiety Scores, and Depression Scores

Group	n	Age (years)		Trait anxiety		State anxiety		PSWQ		BDI	
		M	SE	M	SE	M	SE	M	SE	M	SE
Shock	36	29.1	1.4	32.1	1.4	27.1	1.3	29.4	1.2	1.5	0.3
Airblast	36	29.3	1.3	30.0	0.9	27.0	0.9	32.7	1.2	1.0	0.3

Note. PSWQ = Penn State Worry Questionnaire; BDI = Beck Depression Inventory.

intense (60 psi) jet of air delivered by plastic tubing at the level of the larynx as described in Grillon and Ameli (1998).

At the end of the experiment, participants were asked to rate their overall subjective anxiety in the N, P, and U conditions and the aversiveness of the shock or airblast on an analog scale ranging from 1 (*not at all*) to 5 (*extremely*). Note that the anxiety rating did not attempt to distinguish between the presence and absence of the cues.

Data Analysis

Peak amplitude of the blink reflex was determined in the 20–100-ms time frame following stimulus onset relative to baseline (average baseline electromyograph level for the 50 ms immediately preceding stimulus onset). SCRs to the cues were calculated by subtracting the SCL at onset from the maximum SCL within 1–5 s after cue onset. NS-SCRs were defined as increases of at least .05 μS. SCLs, NS-SCR, HR, and FPV were analyzed during the 2nd minute of the 2-min baseline period and during 30-s stimulus-free periods in each condition. SCR and SCL scores were log-transformed to attain statistical normality. For each physiological variable, the data were averaged for each condition over blocks. The magnitude of the eyeblink was also analyzed by means of *t* scores, after standardization within subjects. Because similar results were obtained with the raw scores and with the *t* scores for within-subjects comparisons, only results of the raw scores are presented. The data were analyzed with multivariate analyses of variance (MANOVA) followed by discriminant analyses or/ and univariate analyses of variance (ANOVA).

Results

Baseline Activity

Results for each physiological variable recorded prior to the actual threat experiment are shown in Table 2. These data were analyzed by means of MANOVA, with all five variables entered as dependent variables, and group (shock, airblast) and sex (male, female) as between-subject variables. Results from the MANOVA yielded only a significant multivariate effect for group: Pillai's trace, $F(5, 55) = 2.56$, $p < .03$. Univariate ANOVAs were

Table 2

Mean Baseline for Startle, Skin Conductance Level (SCL), Finger Pulse Volume (FPV), Nonspecific Skin Conductance Response (NS-SCR), and Heart Rate (HR)

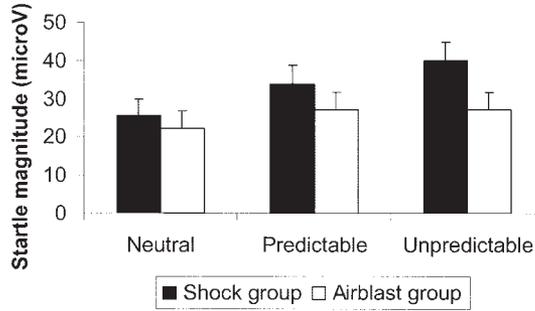| Dependent variables and group	M		SE	
	Men	Women	Men	Women
Startle (μV)				
Shock	46.4	56.9	8.6	11.6
Airblast	34.8	33.0	9.6	9.6
SCL (log μS)				
Shock	6.1	5.4	3.3	1.6
Airblast	4.8	5.3	1.6	2.1
FPV (μV)				
Shock	21.8	19.5	4.1	5.1
Airblast	34.5	22.5	4.6	4.6
NS-SCR (N per 30 s)				
Shock	3.8	2.9	0.7	1.0
Airblast	1.3	1.8	0.8	0.8
HR (beats per minute)				
Shock	64.5	68.4	2.5	3.0
Airblast	66.5	69.7	3.4	3.4

conducted as follow-up analyses to examine how the two groups differed on each of the dependent variables. Univariate ANOVAs were preferred to discriminant function analysis given the small correlations that were found between the dependent variables (see Field, 2000). Follow-up univariate analyses for each dependent variable revealed only higher NS-SCRs in the shock group compared to the airblast group, $F(1, 62) = 4.60$, $p < .03$. There were nonsignificant trends for larger startle magnitude, $F(1, 62) = 3.20$, $p < .08$, and smaller FPV, $F(1, 62) = 2.80$, $p = .10$, in the shock group compared to the airblast group.

Threat Phase: Responses in the Absence of Cues (Contextual Fear)

Results for each physiological variable during the intervals between cues (for startle) or during the 30-s stimulus-free periods (for HR, SCL, NS-SCR, FPV) were analyzed with separate MANOVAs. Levels of condition (N, P, U) were entered as within-subject variables, and group (shock, airblast) and sex (male, female) as the between-subject variables. Significant results from the MANOVAs were then examined with follow-up discriminant function analysis. Given the high correlation between the levels of condition (N, P, and U), it was decided to follow up with discriminant function analysis rather than univariate ANOVAs (for a review, see Field, 2000).

For startle, MANOVA found a significant multivariate effect for group: Pillai's trace, $F(3, 68) = 4.61$, $p = .005$. Discriminant function analysis resulted in one significant function: Wilks' lambda $= .832$, $\chi^2(3, N = 72) = 10.76$, $p = .013$. The relationships between the conditions were investigated by looking at the canonical coefficients in the structure matrix. Values of this matrix are comparable to factor loadings and indicate the nature of the function. Coefficients for U, P, and N were .29, .08, and $-.02$, respectively. Using the recommendation by Bray and Maxwell (1985; Field, 2000) that the dependent variables with the highest canonical correlation coefficients contribute most to group separation, we reasoned that U was more important than P, and N, in discriminating among groups. Because there were only two groups, inspection of the centroïds (mean value for the function) showed that the group who received shock was most affected by the U condition (group centroïds $= .52$), compared to the group who received airblast (group centroïds $= -.37$). This effect is shown in Figure 1, which illustrates the different pattern of startle potentiation in the two groups. It can be seen that blinks evoked in the absence of the cues were potentiated in the predictable and unpredictable threat conditions (relative to no aversive stimulus) in both groups. However, while startle increased linearly from the N to the P to the U condition in the shock group, in the airblast group, startle potentiation in the U conditions was not increased with respect to the P condition. This group difference was also confirmed by a univariate analysis that showed a significant Group $\times$ Condition linear trend (over N, P, U), $F(1, 66) = 14.20$, $p < .001$.

MANOVA did not reveal any significant multivariate effect for group for any other dependent physiological measure. This suggested that the two groups did not differ in their responses across the N, P, and U conditions. Physiological responses across conditions were therefore investigated for the existence of possible linear or quadratic trends. Mixed-design ANOVA with condition

Figure 1. Startle magnitude in the absence of cues (during intertrial interval) in the no aversive stimulus (neutral; N), predictable (P), and unpredictable (U) conditions in the shock and airblast groups. The statistical analysis shows a significant Group × Condition linear trend due to progressively greater group differences from the N to the P to the U condition. Error bars represent standard error.

(N, P, U) as a within-subject variable, and group (shock, airblast) and sex (male, female) as between-group variables was performed on each of the dependent variables. The results for SCL, NS-SCR, HR, and FPV are shown in Figure 2.

For SCL, NS-SCR, HR, and FPV, there was a main effect of condition (all $ps < .01$), which was qualified by significant qua-

dratic trends (all $ps < .01$). The quadratic trends reflected higher SCL, a greater number of NS-SCRs, faster HR, and lower FPV in the P and U condition compared to the N condition.

Threat Phase: Responses During Cues (Explicit Cued Fear)

For startle, MANOVA found a significant multivariate effect for group: Pillai's trace, $F(3, 56) = 2.89$, $p < .05$, and a multivariate effect for sex: $F(3, 56) = 3.72$, $p < .02$. Follow-up ANOVAs revealed significantly greater startle potentiation during the threat cue in the P condition in the shock group compared to the airblast group (see Figure 3, top), $F(1, 58) = 6.92$, $p < .02$, and in women compared to men (see Figure 4), $F(1, 58) = 5.97$, $p < .02$.

For SCR, MANOVA found a significant multivariate effect for group: Pillai's trace, $F(3, 66) = 5.74$, $p < .002$. Follow-up univariate ANOVAs showed greater SCR to the threat cue in the P condition in the shock group compared to the airblast group (Figure 3, bottom), $F(1, 68) = 8.28$, $p = .005$.

Subjective Reports

Retrospective ratings of overall anxiety during the N, P, and U conditions were very similar to the pattern of startle reactivity in the absence of the cues (see Figure 5). The statistical analysis of
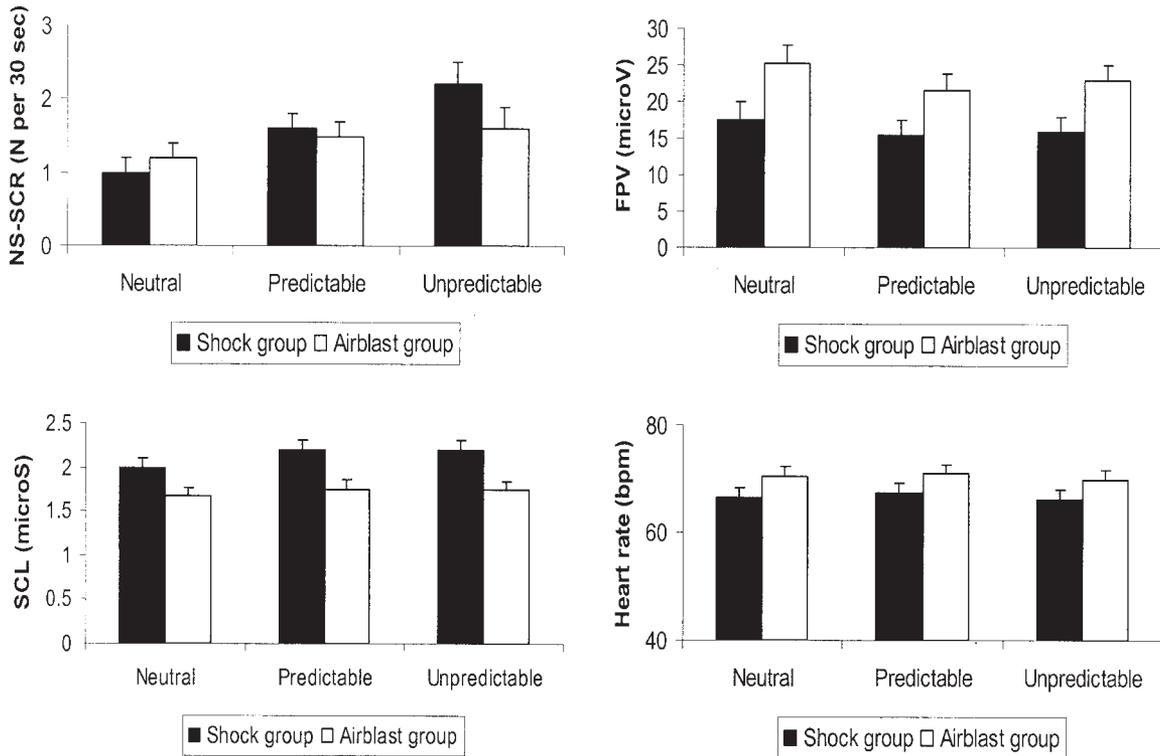

Figure 2. Physiological activity during stimulus-free periods in the no aversive stimulus (neutral; N), predictable (P), and unpredictable (U) conditions in the shock and airblast groups. The statistical analysis showed a significant Group × Quadratic trend for each variable that was due to difference in responses during the U and P conditions compared to the N condition. Error bars represent standard error. SCL = skin conductance level; NS-SCR = nonspecific skin conductance response; FPV = finger pulse volume; bpm = beats per minute.
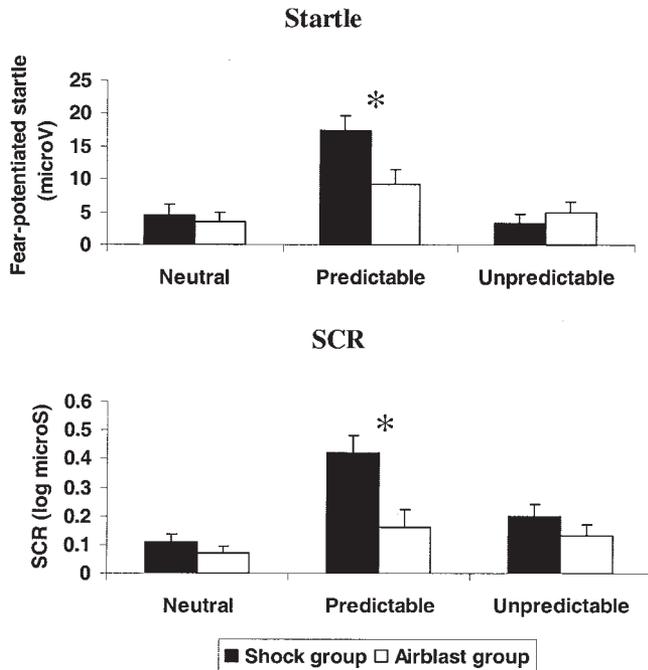
Startle

SCR

Figure 3. Physiological response to or during the cues in the no aversive stimulus (neutral), predictable, and unpredictable conditions in the shock and airblast groups. Top: Fear-potentiated startle, expressed as the difference in startle magnitude from the intertrial interval to the cue period. Bottom: Skin conductance response (SCR) to the cues. Error bars represent standard error. Asterisks indicate significant group differences ($p < .05$).

subjective ratings revealed a significant Group × Condition interaction, $F(2, 136) = 7.40$, $p < .001$, and a Group × Condition linear trend, $F(1,068) = 11.40$, $p < .001$, reflecting a progressively greater group difference in anxiety from the N to the P to the U condition.

On a scale of aversiveness from 1 (*not at all*) to 5 (*extremely*), the shock was rated as more unpleasant compared to the airblast, $F(1, 68) = 37.10$, $p < .001$. Mean ratings were 2.8 (*SEM* = 0.12) and 1.8 (*SEM* = 0.12), in the shock and airblast groups, respectively.
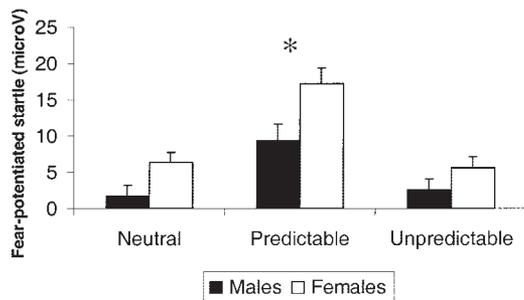

Figure 4. Fear-potentiated startle during the cues in the no aversive stimulus (neutral), predictable, and unpredictable conditions in males and females. Asterisk indicates a significant group difference ($p < .05$). Error bars represent standard error.
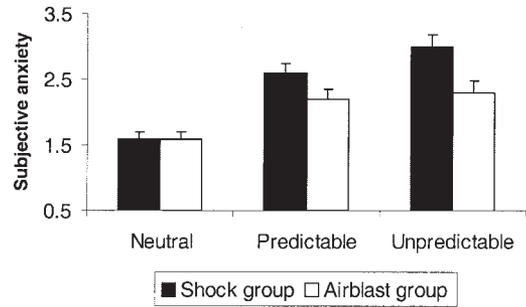

Figure 5. Subjective reports of anxiety in the no aversive stimulus (neutral; N), predictable (P), and unpredictable (U) conditions in the shock and airblast groups. There was a significant Group × Condition linear trend, reflecting progressively greater group difference subjective anxiety from the N to the P to the U condition. Error bars represent standard error.

Discussion

This study compared physiological and subjective measures of anxiety induced by predictable and unpredictable delivery of a shock and a less aversive airblast. There were three key findings:

1. Baseline physiological activity differed in the shock group compared to the airblast group. There was greater physiological arousal, especially NS-SCR, and to a lesser extent startle and FPV, in the shock group compared to the airblast group. These results suggest that the nature of the threat affected emotional arousal prior to participants' being at risk of receiving the aversive stimuli.

2. Two different types of physiological responses were identified in the P condition: a phasic response to the threat cue and a more sustained response (relative to the N condition) in the absence of the cues.

3. This sustained aversive response was enhanced by unpredictability in the shock group, but not in the airblast group (based on startle measures). These results indicate that aversive motivation is not always affected by predictability and that unpredictability is not intrinsically anxiogenic (Staub et al., 1971).

Several studies have failed to show an effect of predictability (Geer & Maisel, 1972; Glass et al., 1973; Price & Geer, 1972; Vogeltanz & Hecker, 1999). The present study suggests that such a failure could be a function of using either an inadequate unconditioned stimulus or physiological measures that may not be sensitive enough to aversive motivation. Concerning the nature of the unconditioned stimulus, an effect of predictability on physiological responses has been found with shocks in the present study and by others (Price & Geer, 1972), but not with CO_2, loud noises, or disturbing pictures (Lejuez et al., 2000; Taylor et al., 1999; Vogeltanz & Hecker, 1999). Shock was more anxiogenic than the airblast, on the basis of subjective rating and physiological responses during the threat cue, suggesting that unpredictability adds an aversive dimension to emotional reactions only if it is associated with stimuli that are sufficiently feared (Mineka & Kihlstrom,

1978). Alternatively, shocks are associated with real pain or with the anticipation of pain. Pain or its anticipation may be critical to obtain an effect of predictability. To what extent the effect of predictability generalizes to other aversive stimuli will need to be determined by future studies. Given the role of CO_2 as a panic-relevant stimulus (Papp et al., 1989), and the finding that predictable CO_2 is preferred over unpredictable CO_2 (Lejuez et al., 2000), it would be interesting to examine whether unpredictable CO_2 induces more contextual fear than predictable CO_2.

Only startle differentiated the predictable and unpredictable conditions in the shock group. These results suggest that some physiological measures are more sensitive to fluctuations in anxiety caused by unpredictability than others. Price and Geer (1972) found twice as many NS-SCRs in participants anticipating unpredictable shocks versus predictable shocks. In contrast, Baker and Stephenson (2000) did not report consistent differences in HR between anticipation of predictable versus unpredictable shocks. HR is sensitive to attentional, emotional, and behavioral demands. It is slowed down by attention to the environment, but it can be increased by fear (Lacey, 1967). These opposite effects on HR may have interacted dynamically to lead to the present finding of faster HR in the P condition compared to the two other conditions. With regard to the skin conductance, Lejuez et al. (2000) found that SCL did not differentiate between predictable and unpredictable administration of an anxiogenic mixture of 20% CO_2-enriched air, although participants in this study preferred predictable over unpredictable exposure to CO_2.

From a methodological viewpoint, an important finding is the substantial level of anxiety in the "safe" periods (i.e., in the absence of the cue) of the P condition compared to the N condition. This effect was found with all the physiological measures. In "threat" experiments, threat periods have usually been compared to safe periods (Grillon et al., 1991; Riba et al., 2001). The present result points to a substantial degree of anxiety still present in these safe periods. It is conceivable that vulnerable individuals are less able than others to reduce anxiety during safe periods. Consistent with this view, we have reported sustained elevation in startle, including during safe periods, in patients with anxiety disorders throughout experiments that include administration of electric shocks (Grillon et al., 1994; Grillon, Morgan, et al., 1998). It is likely that this increased startle reactivity in anxious individuals is due to anticipatory anxiety caused by the stressful experimental context (Grillon & Morgan, 1999). Our objective is to assess the effect of predictability in anxious individuals using the present design. We predict the greatest differentiation between anxious and nonanxious participants will be in the unpredictable condition.

Unpredictable aversive stimuli are particularly debilitating (Mineka et al., 1984; Mineka & Kihlstrom, 1978; Overmier & Wielkewicz, 1983). The present results provide clues as to why unpredictable aversive events are more stressful and, in the long term, may be more harmful than predictable aversive events (Mineka & Kihlstrom, 1978). To the extent that startle reflects aversive motivation (Grillon & Baas, 2003; Davis et al., 1993), unpredictable shock resulted in a higher level of sustained anxiety compared to predictable shock, which was characterized by a surge of fear prompted by the signal for danger. It is likely that the stressful nature of unpredictability is caused by the sustained level of anxiety it engenders. Predictable aversive events may be less

stressful because they offer periods of relative relief when the threat cue is absent. This account is consistent with the safety-signal hypothesis (Seligman & Binik, 1977) that considers the absence of shock cues in a predictable condition as a period of safety.

There was a sex difference in reactivity to the cues, with women showing greater startle potentiation than men. This result should be interpreted with caution, because we have usually been unable to find a reliable sex difference in healthy participants in our previous studies (Grillon & Davis, 1997; Grillon, 2002a). One possibility is that the present design facilitates the identification of sex difference in aversive motivation. Such a difference, if confirmed by future studies, could be meaningful given the well-established higher rate of mood and anxiety disorders among females relative to males (Kessler et al., 1994).

A limitation of the study is that because aversive stimuli were administered in the P and U conditions, but not in the N condition, physiological responses in the N conditions may not be comparable to those of the two threat conditions. In particular, aversive stimuli could sensitize responses to a subsequently delivered startle stimulus (Davis, 1989). However, this does not appear to be the case. A reanalysis of the data in the P and U conditions revealed no significant difference in startle reactivity for startle stimuli presented before and after an aversive stimulus.

In summary, the present results show that predictability influences startle responses during shock anticipation in humans. Both the debilitating effect of unpredictable shock and the preference for predictable danger may be related to the finding that unpredictable danger leads to a more sustained level of anxiety than predictable danger. In this regard, contextual fear to unpredictable danger may be an experimental model for the symptoms of sustained anxious apprehension that cuts across anxiety disorders. If unpredictability is a causal factor in the development of anxiety disorders (Barlow, 2000), understanding the origin of unpredictability and of its consequences will likely provide clues as to the nature of these conditions. The present experimental design provides a novel approach for clinical, psychopharmacological, and brain imaging assessment of aversive motivation.

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